University of Alberta

Mathematical model of influenza for interspecies transmission between humans and pigs, and its role in human influenza infection.

by

Jungmin Lee

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Master of Science

in Applied Mathematics

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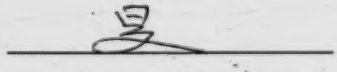

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled **Mathematical model of influenza for interspecies transmission between humans and pigs, and its role in human influenza infection** submitted by **Jung Min Lee** in partial fulfillment of the requirements for the degree of **Master of Science** in Mathematics Biology and Ecology.

Dr. James Muldowney (Chair)

Dr. Joseph So (Supervisor)

Dr. Henry van Roessel

Dr. Peter Schiavone (Mechanical Engineering)

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Abstract

For influenza viruses, the species barrier between pigs and humans is relatively low when compared with the barrier between birds and humans. Therefore, pigs may function as intermediates and mixing vessels for the creation of new pandemic strains, either by introduction of avian viruses into pigs in toto or by reassortment of individual genes during antigenic shifts. In this thesis, we formulate and analyze cross–infection models between human and pig species. In particular, two directions are considered. The first is as b_1 and b_2, the strength of cross–barrier infection, change. The second is to include temporal delay in one of ithe two populations. In the absense of time delay, the model whose b_1 and b_2 are constant seems to converge to an equilibrium (either the no–disease or the endemic one). The model with a delay term is formulated under the assumption that there is loss of immunity after a certain period of time for the human population but no time delay in the pig population due to their relatively short lifecycle. We show that the delay model may have periodic solutions.

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Chapter 1

Introduction

1.1 Influenza

Influenza is a highly contagious acute respiratory disease. It is globally important because it has caused epidemics and pandemics in humans for centuries. Normally the infection is over after a couple of days, but sometimes deaths occur in elderly people and in smokers and those with chronic heart and lung disease. Influenza in man occurs in two epidemiological forms. The first is pandemic influenza, which results from the emergence of a new influenza A virus antigenic shift to which the population possesses little or no immunity. It therefore normally spreads with high attack rates throughout all parts of the world. The second is interpandemic influenza, occurring as sporadic infections, a localized outbreak or endemic, the latter representing an outbreak in a given community which usually occurs abruptly, peaks within 2–3 weeks, lasts 5–6 weeks, and is associated with significant drift of the surface antigens. Epidemics occur virtually every year almost exclusively in the winter months in the northern hemisphere (October to April), and in May to September in the Southern hemisphere. Virological, seroarchaeological and molecular studies have revealed that although

all 15 haemagglutinin and 9 neuraminidase subtypes of influenza A have been isolated from birds in most probable combinations, only a limited number have caused outbreak in human. In general, influenza viruses are species specific, however, whole viruses may occasionally be transmitted from one species to another and genetic reassortment between viruses from two different hosts can create a virus that is infectious to a third host. Influenza viruses are negative sense RNA viruses with single–stranded genomes composed of 8 segments (for influenza A and B, influenza C has 7 segments). The viruses can be divided into a number of subtypes based on differences in the surface glycoproteins, hemagglutinin (H1–H15: 15 subtypes) and neuraminidase (N1–N9: 9 subtypes) [37].

Influenza A

Influenza A viruses are divided into subtypes on the basis of serological and genetic differences in the surface glycoproteins and the genes that encode them. Hemagglutinin (H1–H15: 15 subtypes) and Neuraminidase (N1–N9: 9 subtypes) have been found. Among them, influenza A viruses with hemagglutinin proteins of H1, H2 and H3 subtypes, and neuraminidase proteins of N1 and N2 subtypes have caused epidemic and pandemic in humans. All known subtypes of influenza viruses are found among wild avian species that are the primary reservoirs for the virus. Various subtypes have also been found from pigs, horses, seals, and whales. These avian viruses have been verified to cross species barriers, which means that influenza is not considered an eradicable disease. Therefore control and prevention are important here. Human influenza A viruses causes recurrent epidemic, pandemic and repeated infections in human, which is due to the remarkable variability of the viruses.

Influenza B

The antigenic stability of the surface glycoproteins of influenza B is greater than that of influenza A. Thus outbreaks of influenza B occur among younger age

groups, particularly school–age children. Influenza B virus undergoes antigenic drift but not antigenic shift, therefore, influenza B has not been seen in pandemic form. It resembles influenza A on a smaller scale. It is clinically indistinguishable from influenza A.

Influenza C

Influenza C virus infection is very common among children and elderly people, but because of its mildness it is not recognized as an epidemic and has not been studied as much widely as influenza A and B which are responsible for the vast majority of influenza–related morbidity and mortality. It is a cause of the common cold. It is normally human influenza, but it has been found in pigs in China.

Definition of Pandemic

There are two conditions. First one is that the outbreak of infection spreads throughout the world; a high percentage of individuals are infected resulting in increased mortality rates. Second one is that a pandemic is caused by a new influenza A virus subtype. Both conditions should be satisfied for pandemic.[37, 42]

Antigenic shift

Antigenic shift (big change) results in emergence of a new or recycled subtypes of influenza A virus. Thus, there are only partial immunity of the elderly for recycled subtype (e.g. the subtype of pandemic in 1968 and 1898), otherwise there is no immunity. It causes pandemic.

Antigenic drift

Antigenic drift (small change) is the revolution of existing strains of influenza A and B, which allows new variants to escape immunity from prior influenza infection or vaccination. It has caused interpandemic. Crossreacting antibody is found in many people induced by recent influenza infection, but little or no immunity in infants. Therefore, young children are especially vulnerable and

attack rate (morbidity and mortality) are various up to the degree of revolution.[1, 39]

1.1.1 History of influenza

[50, 37, 42]

The history of influenza is very long. The first appearance of an epidemic through clear influenzal symptoms was in AD1173–4, and Molineux described the next outbreak (1694).

In the 16th century, there were at least three influenza epidemic interpreted, and pandemic occurred in America and Europe during the 17th century. The first pandemic occurred in 1580 from Asia during the summer time, spreaded to Africa and then to Europe. It infected the whole of Europe in a 6–month period and the infection landed in America.

The influenza pandemic in 1729 started in Russia in spring time, embraced all of Europe in a 6–month period and continued over a 3–year period with high death rate. After 40 years the next pandemic started in China in autumn, spreaded via Russia westwards to the whole of Europe in an 8–month period. The total attack rate was estimated at 10 million people.

There was a big pandemic in 1830–33, which began in China in winter, spreaded southwards and across Russia into Europe. The outbreak in America was reported in 1831–32. 20–25% of the population was infected.

The influenza pandemic in 1889 spreaded to all of the world, from central Russia in spring, effected the whole of Europe and some part of northern Africa and reached North America and South America in early 1890. It also reached the whole of Asia. The attack rate was between 25– 50% of the population. 300,000 people died. And there were second and third waves in 1891 and 1892.

These pandemics (Spanish flu) occurred in widely disparate parts of the world

at the same time. The pandemic of 1918–20 killed globally more people in a few months than all the armies of World War I in four years and infected 50% of the population. The pandemic resulted in over 20 million deaths globally. It reached the whole world quickly. It possibly emerged from swine or avian host of a mutated H1N1 virus which is closely related to the virus later found in pigs, and it still infects pigs nowadays.

The influenza pandemic (Asian flu) in 1957 began in the Yunan Province of China, and extended to the whole of China. Next it affected all of Asia, crossed to Australia, North and South America. Then it moved to Europe and Africa. New subtype (H2N2) of influenza A showed up. It possibly came from mixed infection of an animal with human H1N1 and avian H2N2 virus strains, which took place in pigs in Asia. The attack rate was 40–50% of the population, of which 25–30% was clinical disease.

The pandemic (Hong Kong flu) of 1968 originated in China, spreaded globally to Asia, Australia, Europe and America. This pandemic was by a new subtype (H3N2) of influenza A virus, which is considered from dual infection of an animal with human H2N2 and avian H3Nx virus strains in Asia with high probability.

The pandemic (Russian flu) of 1977 appeared world widely and the virus strain (H1N1) was almost identical to the influenza A viruses which circulated from 1947 to 1957. Its reappearance was detected at almost the same time in China and Siberia. From this time, H1N1 and H3N2 virus have co–circulated to the present day in human.

In addition to true pandemics, false alarms–emergences of novel strains with few cases and little human transmissibility have also occurred. Several involved swine influenza viruses (4–6) antigenically related to viruses circulating in some pig populations and linked to viruses of the 1918 pandemic. Incidents of 1976 (Swine flu, H1N1, United States), 1986 (H1N1, Netherlands), 1988 (Swine flu,

H1N1, United States) and 1993 (H3N2, Netherlands) were related with those viruses.

Molecular biologic analysis of viral nucleic acid supports the hypothesis that animals (particularly birds and pigs) may have been the source for (and possibly are a continuing reservoir of) the hemagglutinin and other genes found in viruses from the above pandemics.

1.1.2 Avian influenza

[40, 37]

The first avian influenza (AI) virus was isolated in 1902, although it was not identified as a member of the influenza A virus family until 1955. Antigenic and genetic studies strongly suggest that the 1957 Asian and 1968 Hong Kong pandemic strains were generated by genetic reassortment between human and avian viruses.

The available evidence suggests that avian (H1N1) influenza viruses were transmitted to pigs and are causing significant disease.

Longitudinal studies on wild ducks in Canada established that influenza A viruses are perpetuated in apparently healthy feral ducks. Each of the 9 different neuraminidase (NA) subtypes and 14 of 15 haemagglutinin (HA) subtypes of influenza viruses have been isolated from wild ducks. In wild ducks in the northern Hemisphere, influenza viruses predominate in August and September. Juvenile birds are infected as they congregate in marshalling areas prior to migration, and up to 30% of the birds hatched each year shed influenza viruses in their feces. Viruses shedding continues during early migration, but the frequency of virus isolation falls to a very low level ($< 0.01\%$) by November.

In wild ducks, influenza viruses replicate preferentially in the cells that line the intestinal tract, cause no disease signs, and are excreted in high concentrations in

the faeces. Laboratory studies showed that viruses retained infectivity in faecal material for as long as 30 days at 4 degrees and for 7 days at 20 degrees. Because ducks can shed the virus for up to 30 days, very few passages would be required to maintain the virus in the population.

1.1.3 Influenza in pigs and their role as mixing vessels

[44, 51, 47, 40, 48]

Previous studies have shown that interspecies transmission and genetic reassortment of viruses are associated with the appearance of pandemic influenza. These reassortments may have occurred as a result of transfer of an avian virus to a human host already infected with a human strain. However, the available evidence indicates that influenza viruses of avian origin do not undergo productive replication in humans. Therefore, a more likely explanation for the reassortment events responsible for the 1957 and 1968 pandemic viruses is that mixing viruses occurred in another animal that served as a mixing vessel. Pigs have been suggested to be such an intermediate host wherein influenza genomes of human, porcine, and avian origins can mix.

Pigs possess receptors for both avian and human influenza viruses

Reassortment of viral RNA segments during dual infection with an avian and a human influenza virus provides a mechanism by which a new virus is created. In this way, a virus can be generated that has surface antigens against which the human population does not have neutralizing antibodies and is not protected. In order for reassortment and antigenic shift to occur, a host must be dually infected with an avian and a human virus. Avian influenza viruses do not spread in the human viruses, which do not establish themselves in bird populations; thus, the species barrier between birds and humans is quite tight. However, it is shown that pigs can be infected by avian or human influenza A viruses relatively easily

and that the species barriers between pigs and birds or humans are much less stringent. Therefore, pigs may function as intermediate hosts in establishing new influenza virus lineages in humans.

Avian influenza virus transmission to pigs is a relatively rare event, whereas the transmission of human influenza viruses of the H3N2 subtype is relatively frequent

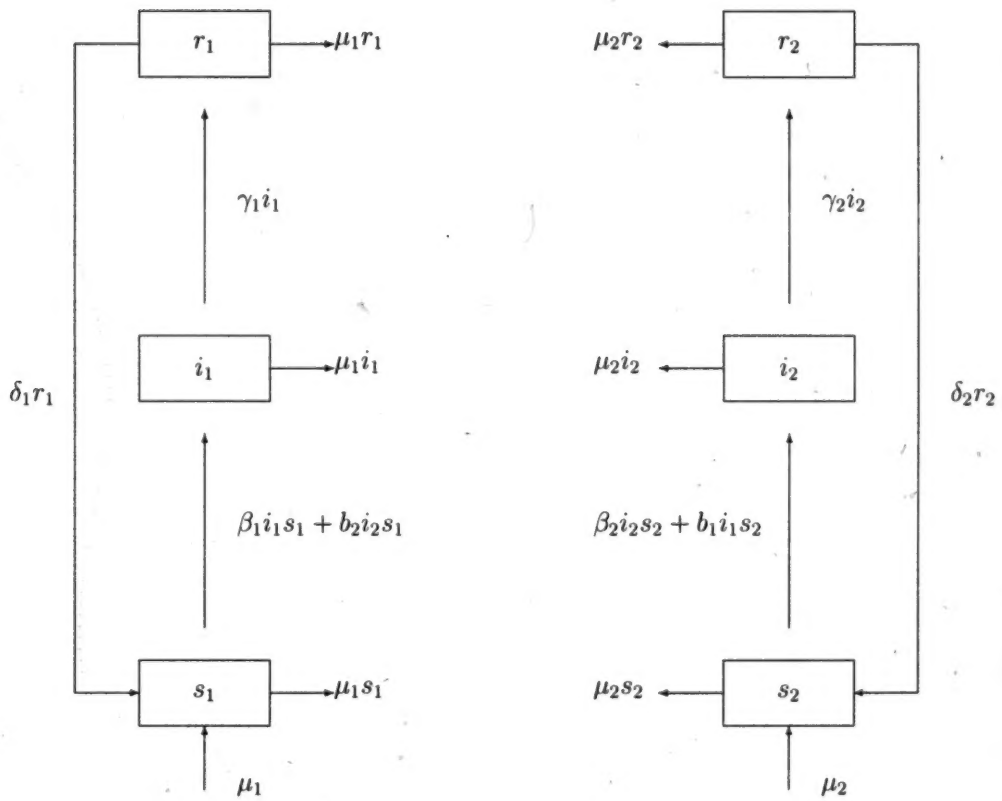
In 1979, an influenza virus with genes all of avian origin was transmitted to pigs in Europe and has continued to spread and cause disease in pigs, viruses whose genome consisted of a mixture of influenza segments of human and avian origins were isolated from pigs in Italy. In addition, direct transfer and replication of a virus has been reported in pigs, and interspecies transmission of influenza viruses from pigs to humans has occurred.

1.2 Mathematical modeling of interspecies transmission of influenza

Each population of size $N_j(t)$ for $j = 1, 2$, which is assumed to be constant, is divided into disjoint classes of individuals who are susceptible, infective and recovered. Human population has temporary immunity, but pigs do not have temporary immunity since its lifetime is shorter than the continuation of immunity in pigs. The dynamical relation among classes of each population is shown in the diagram.

It is assumed that all newborns are susceptible and there is no vertical transmission.

Figure 1.1: Transfer diagram for influenza with two hosts



The following notation for the variables is used throughout. For $j = 1, 2$.

S_j	: susceptible class in population j
I_j	: infectious class in population j
R_j	: recovered class in population j
μ_j	: birth rate and death rate in population j.
	: In pig population, it implies slaughtered rate.
N_j	: total population in population j $(N_j = S_j + I_j + R_j)$
β_{jk}	: infection coefficient of virus from population j to population k
γ_j	: recovery rate in population j
δ_j	: rate of loss of immunity in population j
ϵ_1	: proportion of farm workers in population 1
ς_1	: proportion of people who handle raw pork in population 1
$\beta_{jj}I_j/N_j$	: the force of infection
1	: human population
2	: pig population.

Let

$$\begin{aligned} s_j &= \frac{S_j}{N_j} \\ i_j &= \frac{I_j}{N_j} \\ r_j &= \frac{R_j}{N_j}. \end{aligned} \tag{1.1}$$

Let

$$b_1 = \beta_{12}\epsilon_1$$

$$b_2 = \beta_{21}\epsilon_1 + \beta_{21}\varsigma_1\mu_2$$

In diagram (1.1) we assume that b_1 consists only of direct cross infection $(\beta_{12}\epsilon_1)$ from human and b_2 consists of direct $(\beta_{21}\epsilon_1)$ as well as indirect infection

$(\beta_{21}\varsigma_1\mu_2)$ from pigs. It means that pigs could be infected by farm workers who have influenza infection, but human has two possible ways to get infection from pigs. The first is the infection of farm workers from live pigs, and the other is the infection of those people who handle infected raw pork in slaughterhouse, restaurant and normal kitchen etc. Without the b_1 and b_2 terms, the mathematical model of each population is a standard SIRS model. The case with no time delay is considered in chapter 2, and the general delay case is considered in chapter 3. The following differential equations are derived based on the basis assumptions and the transfer diagram (1.1):

$$
\begin{aligned}
S_1' &= -\mu_1 S_1 - \beta_{11} S_1 I_1/N_1 - \beta_{21}\epsilon_1 S_1 I_2/N_2 - \beta_{21}\varsigma_1\mu_2 S_1 I_2/N_2 + \mu_1 N_1 + \delta_1 R_1 \\
I_1' &= -\mu_1 I_1 - \gamma_1 I_1 + \beta_{11} S_1 I_1/N_1 + \beta_{21}\epsilon_1 S_1 I_2/N_2 + \beta_{21}\varsigma_1\mu_2 S_1 I_2/N_2 \qquad (1.2) \\
R_1' &= \gamma_1 I_1 - \mu_1 R_1 - \delta_1 R_1 \\
S_2' &= -\mu_2 S_2 - \beta_{22} S_2 I_2/N_2 - \beta_{12}\epsilon_1 S_2 I_1/N_1 + \mu_2 N_2 + \delta_2 R_2 \\
I_2' &= -\mu_2 I_2 - \gamma_2 I_2 + \beta_{22} S_2 I_2/N_2 + \beta_{12}\epsilon_1 S_2 I_1/N_1 \qquad (1.3) \\
R_2' &= \gamma_2 I_2 - \mu_2 R_2 - \delta_2 R_2.
\end{aligned}
$$

Using the change of variables (1.1), (1.2)–(1.3) become

$$
\begin{aligned}
s_1' &= -\mu_1 s_1 - \beta_{11} s_1 i_1 - \beta_{21}\epsilon_1 s_1 i_2 - \beta_{21}\varsigma_1\mu_2 s_1 i_2 + \mu_1 + \delta_1 r_1 \\
i_1' &= -\mu_1 i_1 - \gamma_1 i_1 + \beta_{11} s_1 i_1 + \beta_{21}\epsilon_1 s_1 i_2 + \beta_{21}\varsigma_1\mu_2 s_1 i_2 \qquad (1.4) \\
r_1' &= \gamma_1 i_1 - \mu_1 r_1 - \delta_1 r_1 \\
s_2' &= -\mu_2 s_2 - \beta_{22} s_2 i_2 - \beta_{12}\epsilon_1 i_1 s_2 + \mu_2 + \delta_2 r_2 \\
i_2' &= -\mu_2 i_2 - \gamma_2 i_2 + \beta_{22} s_2 i_2 + \beta_{12}\epsilon_1 i_1 s_2 \qquad (1.5) \\
r_2' &= \gamma_2 i_2 - \mu_2 r_2 - \delta_2 r_2.
\end{aligned}
$$

Notice that

$$s_j(t) + i_j(t) + r_j(t) = 1, \text{ for } t \geq 0. \tag{1.6}$$

System (1.4)–(1.5) can be reduced further using (1.6) to

$$\begin{aligned} i_1' &= -\mu_1 i_1 - \gamma_1 i_1 + \beta_{11}(1 - i_1 - r_1)i_1 \\ &\quad + \beta_{21}\epsilon_1(1 - i_1 - r_1)i_2 + \beta_{21}\varsigma_1\mu_2(1 - i_1 - r_1)i_2 \qquad (1.7) \\ r_1' &= \gamma_1 i_1 - \mu_1 r_1 - \delta_1 r_1 \\ i_2' &= -\mu_2 i_2 - \gamma_2 i_2 + \beta_{22}(1 - i_2 - r_2)i_2 + \beta_{12}\epsilon_1 i_1(1 - i_2 - r_2) \qquad (1.8) \\ r_2' &= \gamma_2 i_2 - \mu_2 r_2 - \delta_2 r_2. \end{aligned}$$

1.3 Thesis outline

In Chapter 2, equations (1.7)–(1.8) will be considered. At first, we discuss the case when there is no cross infection. Equations (1.7)–(1.8) become two independent SIRS model. We find the local and global stability of two decoupled SIRS model. After that we return to the case when there exists cross infection (b_j is constant). We discuss the existence and stability of disease–free and endemic equilibrium of this model expressed with (1.7)–(1.8) analytically and numerically. We see numerically that there is no periodic solution. But when we use non–constant b_j, we show numerically that there occurs numerical solution.

In Chapter 3, delay term will be introduced in human population because human keeps immunity for 7–8 years, then starts to lose immunity. For the first, single host SIRS with one delay is to be considered analytically to find that there appears periodic solution due to the delay term newly introduced. From the fact that there occurs periodic solution, we will discuss numerically the effect of this periodic solution on the other host without delay term in coupled SIRS with one delay term. We will see that there appears periodic solution for the pig population due to the delay term of the human population.

In Appendix A, we present some definitions (*stable* , *asymptotically stable* , *globally stable* $\cdots$) and theorems (*Dulac's Criteria*, *Poincaré–Bendixson*, *The Routh–Hurwitz* $\cdots$) Theorem which are used in this thesis

In Appendix B, we present numerical codes used in this thesis, which include dde23, DDE–BIFTOOL, XPPAUT and Campbell(cm.gen).

Chapter 2

Model without Delay

This chapter is based on Liu et al. [32]. In this book, Liu and Levin mention originally the model with coupling of two host populations with no time delay, which is considered in this thesis. Liu et al. [33, 34] considered SIRS model with nonlinear incidence rate. Holt and Pickering [24] discussed two hosts SIS model. Hethcote [20] considered SIRS model with temporary immunity.

Note 1: SIR model is that the population under consideration is divided into three disjoint classes which change with time t (1. The susceptible class consists of those individuals who can incur the disease but not yet infective. 2. The infective class consists of those who are transmitting the disease to others. 3. The recovered class consists of those who are recovered from the susceptible–infective interaction with immunity.)

Note 2: When the immunity is temporary, then after for a while the recovered individual return to the susceptible, which makes SIRS model.

Note 3: When the period of immunity is zero, then the recovered individual return to the susceptible as soon as he/she joins the recovered class, which makes SIS model. There is no recovered class.

Note 4: When we introduce incubation period before individual moves from sus-

ceptible class to infective class, We can deal with SEIR model.

In this chapter, we assume that there is no delay. Then the dynamical model is written by equations (1.7) and (1.8). When b_1 and b_2 are zero, the equations (1.7) and (1.8) become two decoupled differential system. At first, b_1 and b_2 are considered zero. Next we consider them none zero constant case, and at last none constant case is mentioned.

2.1 No cross infection

When the cross infection (between humans and pigs) terms, b_1 and b_2, are zero, system (1.4)–(1.5) is decoupled into two simple SIRS (c.f. Brauer [4], Hethcote [20], Levin [28] and Murray [36]) models, each of which is of the form:

$$\begin{aligned} s' &= -\mu s - \beta si + \mu \\ i' &= -\mu i - \gamma i + \beta si \\ r' &= \gamma i - \mu r - \delta r. \end{aligned} \tag{2.1}$$

Since

$$s(t) + i(t) + r(t) = 1, \text{ for } t \geq 0, \tag{2.2}$$

system (2.1) can be reduced to:

$$\begin{aligned} i' &= -\mu i - \gamma i + \beta i(1 - i - r) \\ r' &= \gamma i - \mu r - \delta r. \end{aligned} \tag{2.3}$$

Definition of global stability. *See Appendix.*

Theorem. If $\sigma := \beta/(\mu + \gamma) > 1$, system (2.3) has a globally stable positive equilibrium (i^*, r^*). Otherwise, the trivial equilibrium $(i_0, r_0) := (0, 0)$ is globally stable for (2.3).

Proof. *Existence of endemic equilibrium*

Setting the right hand side of (2.3) to zeroes and solve for i and r, we get that either $i = 0$ or $i = i^*$, where

$$i^* = (1 - 1/\sigma)/(1 + \gamma/(\mu + \delta)) = \frac{(\beta - \mu - \gamma)(\mu + \delta)}{\beta(\mu + \gamma + \delta)}. \tag{2.4}$$

Also, $r = 0$ when $i = 0$ and $r = r^*$, where

$$r^* = \gamma i^*/(\mu + \delta) = \frac{(1 - 1/\sigma)}{((\mu + \delta)/\gamma + 1)} = \frac{\gamma(\beta - \mu - \gamma)}{\beta(\mu + \delta + \gamma)}, \tag{2.5}$$

when $i = i^*$. This shows that the endemic (positive) equilibrium (i^*, r^*) exists when and only when $\sigma > 1$.

Stability of the disease-free equilibrium $(0, 0)$

Linearizing system (2.3) about the origin $(0, 0)$, we get the Jacobian matrix:

$$\mathbf{J} = \begin{pmatrix} \beta - (\mu + \gamma) & 0 \\ \gamma & -(\mu + \delta) \end{pmatrix} = \begin{pmatrix} (\mu + \gamma)(\sigma - 1) & 0 \\ \gamma & -(\mu + \delta) \end{pmatrix}. \tag{2.6}$$

$\mathbf{J}$ has two eigenvalues: $\lambda_1 = (\mu + \gamma)(\sigma - 1)$ and $\lambda_2 = -(\mu + \delta)$. When $\sigma < 1$, both λ_1 and λ_2 are negative and hence the origin $(0, 0)$ is locally asymptotically stable provided $\sigma < 1$.

Let D be the triangle $\{(i, r) : i \geq 0, r \geq 0, i + r \leq 1\}$.

Claim. For $\sigma < 1$, all solutions of system (2.3) in the region D approach the disease-free equilibrium $(0, 0)$.

Proof of Claim. Clearly the region D is positively invariant.

When $\sigma \leq 1$, there is unique equilibrium at origin $(0, 0)$. By Theorem 6.8.2 (p. 180)[49], there may be one closed orbit around the origin $(0, 0)$. But such orbit will cross the i-axis and r-axis, and thus violating the positive invariance of the region D. Hence, there is no periodic orbit and the origin is a globally stable equilibrium point, by Poincaré-Bendixson theorem (c.f. [41]).

Non-existence of periodic orbits

When $\sigma > 1$, there are two equilibria: $(0,0)$ and (i^*, r^*). Periodic orbit about $(i_0, r_0) = (0,0)$ is ruled out by the positive invariance of D as before. To show that there is no other periodic orbits, we can apply Dulac's criterion (c.f. [49], [41]).

Let $B(i,r) = 1/i$. Then

$$\begin{aligned} \nabla \cdot (Bf) &= \frac{\partial}{\partial i}(Bi') + \frac{\partial}{\partial r}(Br') \\ &= \frac{\partial}{\partial i}(-\mu - \gamma + \beta(1 - i - r)) + \frac{\partial}{\partial r}(-\gamma - \frac{\mu r}{i} - \frac{\delta r}{i}) \\ &= -\beta - \frac{\mu}{i} - \frac{\delta}{i} \\ &< 0, \end{aligned} \tag{2.7}$$

where $f = (i', r')$. on D except at the origin $(0,0)$. Hence, by Dulac's criteria, (2.3) has no periodic orbit in D.

Stability of the endemic equilibrium

The Jacobian matrix of system (2.3) at the endemic equilibrium point (i^*, r^*) is given by:

$$\mathbf{J} = \begin{pmatrix} -\beta i^* & -\beta i^* \\ \gamma & -(\mu + \delta) \end{pmatrix}. \tag{2.8}$$

Since

$$trace(\mathbf{J}) = -\beta i^* - (\mu + \delta) < 0$$

and

$$det(\mathbf{J}) = \beta i^*(\mu + \delta) + \beta\gamma i^* > 0,$$

therefore the two eigenvalues of $\mathbf{J}$ must have negative real parts. This means that the endemic equilibrium is locally asymptotically stable when it exists, i.e. when $\sigma > 1$.

Combining the asymptotic stability of (i^*, r^*), together with the non–existence of periodic orbits in D, it follows from Poincaré–Bendixson theorem that the endemic equilibrium (i^*, r^*) is globally asymptotically stable.

Figures 2.1–2.2 illustrate the positive invariance of D and the global stability of the equilibria in a single SIRS model as σ changes. It is done using xpp [12].

2.2 Coupled case I: b_j is a constant

When b_j $(j = 1, 2)$ is a positive constant, we can expect cross–infection between the two different hosts: human and pigs. The model equation (1.4)–(1.5) now reads:

$$\begin{aligned}
i_1' &= -\mu_1 i_1 - \gamma_1 i_1 + \beta_{11}(1 - i_1 - r_1)i_1 + \beta_{21}\epsilon_1(1 - i_1 - r_1)i_2 \\
&\quad + \beta_{21}\varsigma_1\mu_2(1 - i_1 - r_1)i_2 \\
r_1' &= \gamma_1 i_1 - \mu_1 r_1 - \delta_1 r_1 \\
i_2' &= -\mu_2 i_2 - \gamma_2 i_2 + \beta_{22}(1 - i_2 - r_2)i_2 + \beta_{12}\epsilon_1(1 - i_2 - r_2)i_1 \\
r_2' &= \gamma_2 i_2 - \mu_2 r_2 - \delta_2 r_2.
\end{aligned} \tag{2.9}$$

2.2.1 Existence and uniqueness of the nontrivial–equilibrium. $(i_1^*, r_1^*, i_2^*, r_2^*)$

Let

$$\begin{aligned}
b_1 &= \beta_{12}\epsilon_1 \\
b_2 &= \beta_{21}\epsilon_1 + \beta_{21}\varsigma_1\mu_2 \\
\beta_1 &= \beta_{11} \\
\beta_2 &= \beta_{22}.
\end{aligned}$$

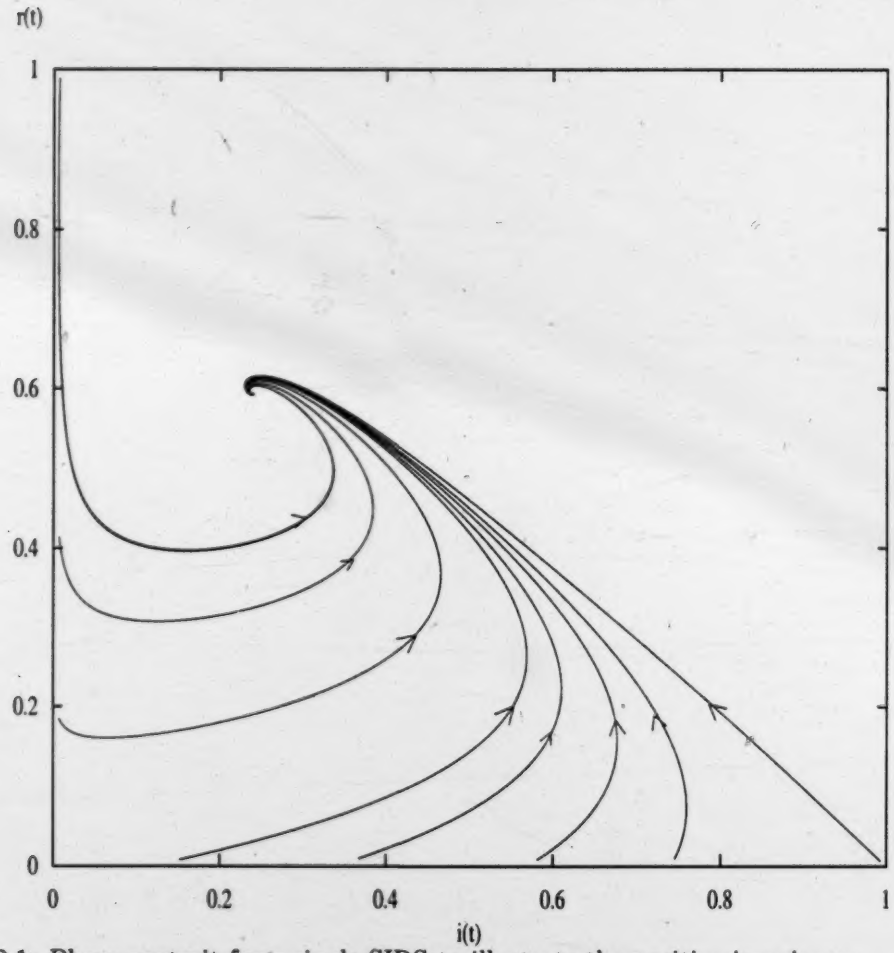


Figure 2.1: Phase portrait for a single SIRS to illustrate the positive invariance of D and the stability of endemic equilibrium (i^*, r^*) when $\sigma = 5.98, \delta = 0.04$.

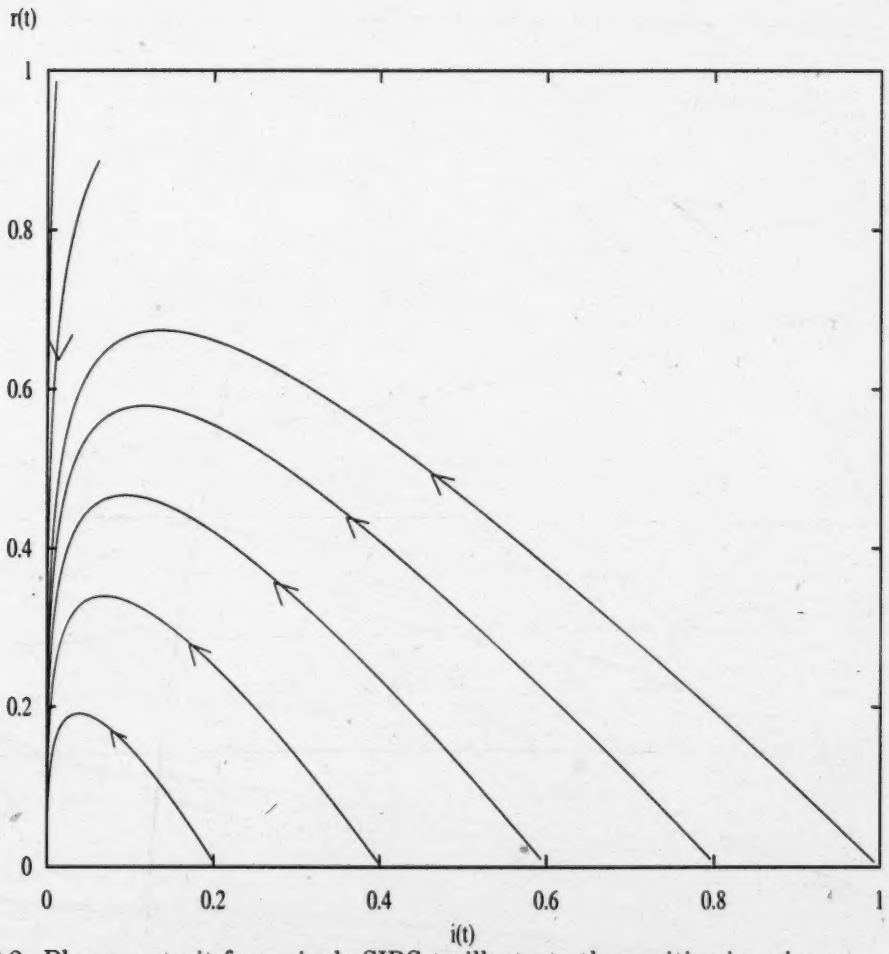


Figure 2.2: Phase portrait for a single SIRS to illustrate the positive invariance of D and the stability of disease–free equilibrium $(0, 0)$ when $\sigma = 0.499, \delta = 0.04$

Then (2.9) becomes

$$\begin{aligned} i_1' &= -\mu_1 i_1 - \gamma_1 i_1 + \beta_1(1 - i_1 - r_1)i_1 + b_2(1 - i_1 - r_1)i_2 \\ r_1' &= \gamma_1 i_1 - \mu_1 r_1 - \delta_1 r_1 \\ i_2' &= -\mu_2 i_2 - \gamma_2 i_2 + \beta_2(1 - i_2 - r_2)i_2 + b_1(1 - i_2 - r_2)i_1 \\ r_2' &= \gamma_2 i_2 - \mu_2 r_2 - \delta_2 r_2. \end{aligned} \tag{2.10}$$

Let $(i_1^*, r_1^*, i_2^*, r_2^*)$ be a non–trivial equilibrium for (2.10). Then

$$r_1^* = h_1 i_1^* > 0, \tag{2.11}$$

where

$$h_1 = \gamma_1/(\mu_1 + \delta_1) \tag{2.12}$$

and

$$r_2^* = h_2 i_2^* > 0, \tag{2.13}$$

where

$$h_2 = \gamma_2/(\mu_2 + \delta_2). \tag{2.14}$$

Let $s_j^* = 1 - i_j^* - r_j^*$. It follows easily from (2.10) that $s_j^* > 0$. Since $s_2^* = 1 - i_2^* - r_2^* = 1 - i_2^* - h_2 i_2^* = 1 - (1+h_2)i_2^*$, which is positive, therefore $i_2^* < 1/(1+h_2) =: H_2$.

Also, $i_j^* \geq 0$ and one of them is positive. i_1 and i_2 can be expressed in terms of each other as follows:

$$\begin{aligned} i_1^* = f_1(i_2^*) &= i_2^*(\mu_2 + \gamma_2 - \beta_2 s_2^*)/(b_1 s_2^*) \\ &= i_2^*(\mu_2 + \gamma_2 - \beta_2(1 - i_2^*/H_2))/(b_1(1 - i_2^*/H_2)) \\ &= (\mu_2 + \gamma_2)i_2^*(\sigma_2 i_2^*/H_2 - (\sigma_2 - 1))/(b_1(1 - i_2^*/H_2)), \end{aligned} \tag{2.15}$$

where

$$\sigma_2 = \beta_2/(\mu_2 + \gamma_2). \tag{2.16}$$

Similarly, we can express i_2^* as a function of i_1^* as follows.

$$\begin{aligned} i_2^* &= f_2(i_1^*) = i_1^*(\mu_1 + \gamma_1 - \beta_1 s_1^*)/(b_2 s_1^*) \\ &= i_1^*(\mu_1 + \gamma_1 - \beta_1(1 - i_1^*/H_1))/(b_2(1 - i_1^*/H_1)) \\ &= (\mu_1 + \gamma_1) i_1^*(\sigma_1 i_1^*/H_1 - (\sigma_1 - 1))/(b_2(1 - i_1^*/H_1)), \end{aligned} \tag{2.17}$$

where $\sigma_1 = \beta_1/(\mu_1 + \gamma_1)$, and $H_1 = 1/(1 + h_1) > i_1^*$.

Therefore i_1^* and i_2^* are positive for a nontrivial equilibrium because of (2.11), (2.13), (2.15) and (2.17)

Set $x_j = i_j^*/H_j$, and $z_j = (\mu_j + \gamma_j)H_j/(b_{3-j}H_{3-j})$, where $j = 1, 2$.

Then equations (2.15) and (2.17) become

$$x_1 = F_1(x_2) = z_2 x_2(1/(1 - x_2) - \sigma_2) \tag{2.18}$$

$$x_2 = F_2(x_1) = z_1 x_1(1/(1 - x_1) - \sigma_1). \tag{2.19}$$

Lemma. For $z > 0$, the function

$$f(x) = zx(1/(1 - x) - \sigma)$$

is convex on$(-\infty, 1)$

Proof.

$$f'(x) = z/(1 - x)^2 - z\sigma \tag{2.20}$$

$$f''(x) = 2z/(1 - x)^3 > 0 \text{ for } x < 1. \tag{2.21}$$

Because the second derivative of f is positive for $x < 1$, elementary calculus shows that $f(x)$ is a concave upwards on the interval $(-\infty, 1)$.

Theorem. A nontrivial equilibrium exists for (2.10) if and only if

(i) $\sigma_1 > 1$ or

(ii) $\sigma_2 > 1$ or

(iii) $\sigma_1 \leq 1, \sigma_2 \leq 1$ and $(1 - \sigma_1)(1 - \sigma_2) < b_1 b_2/((\gamma_1 + \mu_1)(\gamma_2 + \mu_2))$.

Moreover, such an equilibrium is unique when it exists.

Proof. In Figure 2.3, we graph (2.18)–(2.19) on the (x_1, x_2) plane. Note that $F_1(1^-) = +\infty$ and $F_2(1^-) = +\infty$. Due to the parameters, z_1, z_2, σ_1 and σ_2, there are four kinds of graphs in figure 2.3. Among them, (b), (c) and (d) types have nontrivial intersection, which is determined by the initial slope (at the origin) of each function (2.18) and (2.19). The initial slope of the inverse of F_1 is $z_2(1-\sigma_2)$. The initial slope of F_2 is $1/(z_1(1-\sigma_1))$. When the initial slope of (2.18) is greater than or equal to the slope of (2.19)that is figure 2.3 (case (a)), there is only trivial solution.

Therefore, if $z_1(1-\sigma_1) \geq 1/(z_2(1-\sigma_2))$, then there is only the trivial solution (intersection point), meaning case (a). By the definition of z_j, this inequality can be rewritten as:

$$(1-\sigma_1)(1-\sigma_2) \geq b_1 b_2/((\gamma_1+\mu_1)(\gamma_2+\mu_2))$$

which becomes

$$(1-\sigma_1)(1-\sigma_2)(\gamma_1+\mu_1)(\gamma_2+\mu_2) \geq b_1 b_2.$$

In order to have a nontrivial solution, we must be in cases (b),(c) or (d).

Case (b) says that (I) the slope of each function (2.18) and (2.19) should be positive, and (II) the slope of (2.19) should be greater than or equal to the slope of (2.18). These two conditions are equivalent to (iii):

$$\sigma_1 \leq 1, \text{ and } \sigma_2 \leq 1 \text{ and } (1-\sigma_1)(1-\sigma_2)(\gamma_1+\mu_1)(\gamma_2+\mu_2) < b_1 b_2.$$

Cases (c) and (d) say that there is at least one negative initial slope. This is equivalent to (i) $\sigma_1 > 1$ or (ii) $\sigma_2 > 1$.

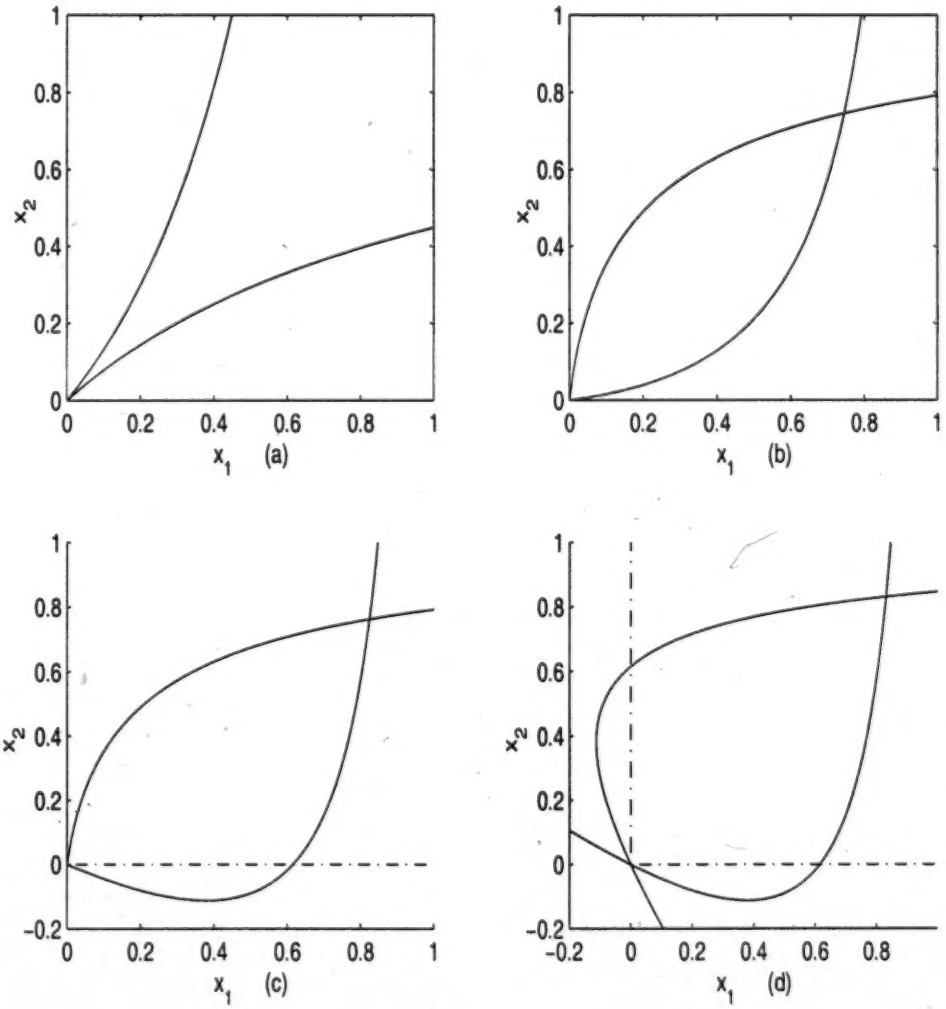


Figure 2.3: As the initial slopes of (2.18)–(2.19) change, there show up four possible types of graph.

2.2.2 Stability of the trivial equilibrium $(0,0,0,0)$

When we linearize (2.10) about the trivial equilibrium, we get the Jacobian matrix

$$\mathbf{J} = \begin{pmatrix} \beta_1 - (\mu_1 + \gamma_1) & 0 & b_2 & 0 \\ \gamma_1 & -(\mu_1 + \delta_1) & 0 & 0 \\ b_1 & 0 & \beta_2 - (\mu_2 + \gamma_2) & 0 \\ 0 & 0 & \gamma_2 & -(\mu_2 + \delta_2) \end{pmatrix}. \tag{2.22}$$

When we exchange r_1 and i_2, we have the block matrix:

$$\hat{\mathbf{J}} = \begin{pmatrix} \beta_1 - (\mu_1 + \gamma_1) & b_2 & 0 & 0 \\ b_1 & \beta_2 - (\mu_2 + \gamma_2) & 0 & 0 \\ \gamma_1 & 0 & -(\mu_1 + \delta_1) & 0 \\ 0 & \gamma_2 & 0 & -(\mu_2 + \delta_2) \end{pmatrix}. \tag{2.23}$$

To find the eigenvalues of $\hat{\mathbf{J}}$, we need to check the two 2×2 matrices:

$$\mathbf{J_1} = \begin{pmatrix} \beta_1 - (\mu_1 + \gamma_1) & b_2 \\ b_1 & \beta_2 - (\mu_2 + \gamma_2) \end{pmatrix}. \tag{2.24}$$

and

$$\mathbf{J_2} = \begin{pmatrix} -(\mu_1 + \delta_1) & 0 \\ 0 & -(\mu_2 + \delta_2) \end{pmatrix}. \tag{2.25}$$

Clearly, $\mathbf{J_2}$ has two negative real eigenvalues $\lambda_3 := -(\mu_1+\delta_1)$ and $\lambda_4 := -(\mu_2+\delta_2)$.

Let

$$a_1 = -\beta_1 + (\mu_1 + \gamma_1)$$
$$a_2 = -\beta_2 + (\mu_2 + \gamma_2).$$

Then the characteristic equation of $\mathbf{J_1}$ is given by:

$$(\lambda + a_1)(\lambda + a_2) - b_1 b_2 = 0 \tag{2.26}$$

which can be simplified to

$$\lambda^2 + (a_1 + a_2)\lambda + a_1 a_2 - b_1 b_2 = 0. \tag{2.27}$$

The two eigenvalues of $\mathbf{J_1}$ have negative real parts (and hence the trivial equilibrium is asymptotically stable) if and only if $a_1 + a_2 > 0$ and $a_1 a_2 - b_1 b_2 > 0$ The first condition is equivalent to

$$(1 - \sigma_1)(\gamma_1 + \mu_1) + (1 - \sigma_2)(\gamma_2 + \mu_2) > 0. \tag{2.28}$$

The second condition is equivalent to

$$(\gamma_1 + \mu_1)(\gamma_2 + \mu_2)(1 - \sigma_1)(1 - \sigma_2) > b_1 b_2, \tag{2.29}$$

since $\sigma_j = \beta_j/(\mu_j + \gamma_j)$ $(j = 1, 2)$.

There are four cases to consider:

(i) $\sigma_1 \geq 1, \sigma_2 \geq 1$;

(ii) $\sigma_1 \geq 1, \sigma_2 < 1$;

(iii) $\sigma_1 < 1, \sigma_2 \geq 1$; and

(iv) $\sigma_1 < 1, \sigma_2 < 1$.

Clearly case (i) fails to satisfy (2.28). Also cases (ii) and (iii) do not satisfy (2.29). Only in case (iv) that we are be able to find parameters which will satisfy (2.28) and (2.29) simultaneously. Under case (iv), since $\sigma_j > 0$, we can modify the equation (2.29) as:

$$(\gamma_1 + \mu_1)(\gamma_2 + \mu_2) > (\gamma_1 + \mu_1)(\gamma_2 + \mu_2)(1 - \sigma_1)(1 - \sigma_2) > b_1 b_2, \tag{2.30}$$

since

$$0 < (1 - \sigma_1) < 1.$$

So a necessary condition for the trivial equilibrium to be asymptotically stable is that

$$(\gamma_1 + \mu_1)(\gamma_2 + \mu_2) > b_1 b_2, \tag{2.31}$$

Next we will give some sufficient condition for the global stability of disease–free (trivial) equilibrium. Let $D = \{(i_1, r_1, i_2, r_2) : i_j \geq 0, r_j \geq 0, i_j + r_j \leq 1 \text{ for } j = 1, 2\}$, i.e. D is the product of two triangles.

Claim. The region D is positively invariant.

Proof of Claim. If D is not positively invariant. Then there exists a solution of (2.10) such that $i_j(0)$ and $r_j(0) \in D$ but $i_j(T)$ or $r_j(T) \notin D$ for some $T > 0$. It means that $i_j(t)$ or $r_j(t)$ cross the boundary of D for some $t > 0$. We try to show that D is positively invariant by showing that no $i_j(t)$ or $r_j(t)$ cross the boundary of D. On the i_j axis, r_j become zero. Thus we have $r_j' = \gamma_j i_j$, which is positive, which means that a solution of (2.10) cannot cross the boundary of D through i_j axis. Similarly on the r_j axis, i_j become zero. Thus we have $i_j' = -\mu_j i_j - \gamma_j i_j + \beta_j(1-i_j)i_j + b_{3-j}(1-i_j)i_{3-j} = (-\mu_j - \gamma_j + \beta_j(1-i_j))i_j + b_{3-j}(1-i_j)i_{3-j}$,which is positive for $i_j < 0$, since for the first term $-\mu_j - \gamma_j + \beta_j < 0$, and for the second second term $b_{3-j}(1-i_j)i_{3-j} > 0$, which means that a solution of (2.10) cannot cross the boundary of D through r_j axis. On the $i_j + r_j = 1$, $(i_j + r_j)' = -\mu_j(i_j + r_j) - \delta_j r_j < 0$, which means that $(i_j + r_j)$ cannot become greater than 1. Therefore D is positively invariant.

Theorem. If $\beta_1 + b_1 < \mu_1 + \gamma_1$ and $\beta_2 + b_2 < \mu_2 + \gamma_2$, then all solution of system (2.10) in the region D approach the disease–free equilibrium $(0, 0, 0, 0)$.

Proof. Consider the Lyapunov function $V(i_1, r_1, i_2, r_2) = i_1 + i_2 > 0$ for all $i_1, i_2 > 0$. Then the trajectory derivative of V is given by:

$$
\begin{aligned}
V' &= i_1' + i_2' \\
&= \beta_1 i_1(1 - i_1 - r_1) - (\mu_1 + \gamma_1) i_1 + b_2 i_2(1 - i_1 - r_1) \\
&\quad + \beta_2 i_2(1 - i_2 - r_2) - (\mu_2 + \gamma_2) i_2 + b_1 i_1(1 - i_2 - r_2) \\
&= i_1(-\mu_1 - \gamma_1 + \beta_1(1 - i_1 - r_1) + b_1(1 - i_2 - r_2)) \qquad (2.32) \\
&\quad + i_2(-\mu_2 - \gamma_2 + \beta_2(1 - i_2 - r_2) + b_2(1 - i_1 - r_1)) \\
&\leq i_1(-\mu_1 - \gamma_1 + \beta_1 + b_1) + i_2(-\mu_2 - \gamma_2 + \beta_2 + b_2) \\
&< 0.
\end{aligned}
$$

The last inequality holds since we have assumed $\beta_1 + b_1 < \mu_1 + \gamma_1$ and $\beta_2 + b_2 < \mu_2 + \gamma_2$. This means that as t approaches $+\infty$, i_1 and i_2 approach 0. Therefore, r_1 and r_2 in system (2.10) can be expressed as (as $t \to \infty$):

$$r_1' = -\mu_1 r_1 - \delta_1 r_1 \qquad (2.33)$$

$$r_2' = -\mu_2 r_2 - \delta_2 r_2. \qquad (2.34)$$

When we solve these, we get

$$r_j(t) = r_j(0) \exp\{-(\mu_j + \delta_j)t\},$$

where $j = 1, 2$ and $r_j(0)$ is the initial condition. Hence, each $r_j(t)$ approaches 0 as t approaches ∞. Therefore, by the Lyapunov–LaSalle theorem, the origin $(0, 0, 0, 0)$ is globally stable provided $\beta_1 + b_1 < \mu_1 + \gamma_1$ and $\beta_2 + b_2 < \mu_2 + \gamma_2$.

Remark. The above argument can be made rigorous by using the theory of asymptotically autonomous systems. (c.f. [35])

2.2.3 Local stability of nontrivial equilibrium $(i_1^*, r_1^*, i_2^*, r_2^*)$.

The Jacobian matrix of (2.10) at the endemic equilibrium $(i_1^*, r_1^*, i_2^*, r_2^*)$ is given by:

$$\mathbf{J} = \begin{pmatrix} \beta_1 s_1^* - y_1 - (\mu_1 + \gamma_1) & -y_1 & x_1 & 0 \\ \gamma_1 & -(\mu_1 + \delta_1) & 0 & 0 \\ x_2 & 0 & \beta_2 s_2^* - y_2 - (\mu_2 + \gamma_2) & -y_2 \\ 0 & 0 & \gamma_2 & -(\mu_2 + \delta_2) \end{pmatrix}. \tag{2.35}$$

where $s_j^* = 1 - i_j^* - r_j^*$, $y_j = \beta_j i_j^* + b_{3-j} i_{3-j}^*$, $x_j = b_{3-j} s_j^*$. Let $k = i_2^*/i_1^*$ and $m_j = \mu_j + \delta_j$. Then $\mathbf{J}$ becomes

$$\mathbf{J} = \begin{pmatrix} -x_1 k - y_1 & -y_1 & x_1 & 0 \\ \gamma_1 & -m_1 & 0 & 0 \\ x_2 & 0 & -x_2/k - y_2 & -y_2 \\ 0 & 0 & \gamma_2 & -m_2 \end{pmatrix}. \tag{2.36}$$

Let $\eta_1 = -x_1 k - y_1$ and $\eta_2 = -x_2/k - y_2$. Then the eigenvalues of $\mathbf{J}$ are given by the roots of:

$$0 = det \begin{pmatrix} \eta_1 - \lambda & -y_1 & x_1 & 0 \\ \gamma_1 & -m_1 - \lambda & 0 & 0 \\ x_2 & 0 & \eta_2 - \lambda & -y_2 \\ 0 & 0 & \gamma_2 & -m_2 - \lambda \end{pmatrix}. \tag{2.37}$$

Expanding the determinant, we get the following characteristic equation:

$$\lambda^4 + A\lambda^3 + B\lambda^2 + C\lambda + D = 0, \tag{2.38}$$

where

$$A = m_1 + m_2 - \eta_1 - \eta_2;$$

$$B = y_1\gamma_1 + y_2\gamma_2 - \eta_2 m_1 - \eta_1 m_1 - \eta_2 m_2 - \eta_1 m_2 + m_1 m_2 + \eta_1\eta_2 - x_1 x_2;$$

$$C = \eta_1\eta_2 m_1 - \eta_1 y_2\gamma_2 - \eta_2 y_1\gamma_1 + m_1 y_2\gamma_2$$
$$- \eta_2 m_1 m_2 + \eta_1\eta_2 m_2 - \eta_1 m_1 m_2 + m_2 y_1\gamma_1 - x_1 x_2 m_1 - x_1 x_2 m_2;$$

$$D = y_1\gamma_1 y_2\gamma_2 - \eta_1 m_1 y_2\gamma_2 + \eta_1\eta_2 m_1 m_2 - \eta_2 m_2 y_1\gamma_1 - x_1 x_2 m_1 m_2.$$

Symmetric case

To find the local stability, first we consider the symmetric case. That is $S = S_1 = S_2$, $i = i_1 = i_2$, $y = y_1 = y_2$, $x = x_1 = x_2$, $k = 1$, $m = m_1 + m_2$, $\mu = \mu_1 = \mu_2$, $\gamma = \gamma_1 = \gamma_2$, $\delta = \delta_1 = \delta_2$, therefore $\eta = \eta_1 = \eta_2$.

Jacobian matrix becomes:

$$\mathbf{J} = \begin{pmatrix} \eta - \lambda & -y & x & 0 \\ \gamma & -m - \lambda & 0 & 0 \\ x & 0 & \eta - \lambda & -y \\ 0 & 0 & \gamma & -m - \lambda \end{pmatrix}. \tag{2.39}$$

Expanding the determinent, we get the following characteristic equation:

$$\lambda^4 + A\lambda^3 + B\lambda^2 + C\lambda + D = 0, \tag{2.40}$$

where,

$$\begin{aligned} A &= 2(m - \eta); \\ B &= 2y\gamma - 4\eta m + m^2 + \eta^2 - x^2; \\ C &= 2\eta^2 m - 2\eta m^2 + 2(m - \eta)y\gamma - 2x^2 m; \\ D &= y^2\gamma^2 - 2amy\gamma + \eta^2 m^2 - x^2 m^2. \end{aligned}$$

From here, we use the Routh–Hurwitz criterion [8, 52].

Theorem. In the symmetric case the endemic equilibrium is locally stable.

Proof. A, B, C, D can be written as:

$$\begin{aligned} A &= 2(m - \eta); \\ B &= 2(y\gamma - \eta m) + (m - \eta)^2 - x^2; \\ C &= 2(m - \eta)(y\gamma - \eta m) - 2x^2 m; \\ D &= (y\gamma - am)^2 - x^2 m^2. \end{aligned}$$

Because $m > 0$, $y > 0$, $\gamma > 0$ and $\eta < 0$, and $\eta = -x - y$ one shows easily that A is positive. B is shown to be positive by $(m - \eta)^2 > x^2$. D is positive, since $\eta^2 m^2 > x^2 m^2$ and $(y\gamma - \eta m)^2 > x^2 m^2$.

Finally, we need to show

$$C(AB - C) > A^2 D, \tag{2.41}$$

for local stability, that is all the roots of (2.40) have negative real parts.

Using Maple, we can see the inequality of (2.41). Then :

$$C(AB - C) - A^2 D = \tag{2.42}$$

$$-4(\eta - m + x)(-\eta + m + x)$$

$$(m\eta x^2 + 2\eta^2 m^2 - m^3\eta + m^2 y\gamma - m\eta^3 + y\gamma\eta^2 - 2\eta m y\gamma). \tag{2.43}$$

We have three factors. $\eta - m + x < 0$ by the definition of $\eta = -x - y$, and similarly $-\eta + m + x > 0$. In the last part, all but $m\eta x^2$ are positive since $\eta < 0$, and the third factor is positive because $m\eta x^2 - m\eta^3 > 0$ and the other terms are positive. Therefore the inequality (2.41) is verified. By the Routh–Hurwitz criterion [8, 52], we proved the theorem.

General case

Conjecture. In general case the endemic equilibrium is locally asymptotically stable.

As before A, B, C, D can be written as:

$$A = (m_1 - \eta_1) + (m_2 - \eta_2),$$
$$B = (y_1\gamma_1 - \eta_1 m_1) + (y_2\gamma_2 - \eta_2 m_2) + (m_1 - \eta_1)(m_2 - \eta_2) - x_1x_2,$$
$$C = (m_1 - \eta_1)(y_2\gamma_2 - \eta_2 m_2) + (m_2 - \eta_2)(y_1\gamma_1 - \eta_1 m_1) - x_1x_2(m_1 + m_2),$$
$$D = (y_1\gamma_1 - \eta_1 m_1)(y_2\gamma_2 - \eta_2 m_2) - x_1x_2m_1m_2.$$

Because $m_1 > 0,\ m_2 > 0,\ y_1 > 0,\ y_2 > 0,\ \gamma_1 > 0$ and $\gamma_2 > 0$,
we have $\eta_1 < 0$ and $\eta_2 < 0$. Therefore one sees easily that A is positive. B is shown to be positive because by $|\eta_1| > |x_1|$ and $|\eta_2| > |x_2|$, $(m_1 - \eta_1)(m_2 - \eta_2) > x_1x_2$. D is positive, owing to $\eta_1\eta_2 > x_1x_2$.

According to the Routh– Hurwitz criterion [8, 52], we need to show

$$C(AB - C) > A^2D, \tag{2.44}$$

in order to establish local stability.

When we expand $C(AB-C)-A^2D$ with $x_1,\ x_2,\ y_1,\ y_2,\ k,\ \mu_1,\ \mu_2,\ \gamma_1,\ \gamma_2$, there are 372 positive terms and 9 negative terms.

Using Maple [18] and the parameters in table 2.2 with $\mu_1 = 0.00004$, $\mu_2 = 0.004$, we have following unique endemic equilibrium:

symbol	value	symbol	value
i_1^*	0.11574662283275188132	i_2^*	$0.55948930436823675786e-1$
r_1^*	0.69309354989671785224	r_2^*	0.6993616304602959473 3

Hence $C(AB - C) - A^2D = .28375093779383370730e - 9$

For the global theorem, see Appendix A.

Note: We made attempt to treat the global stability problem using the threorem at the end of Appendix but, we were not successful in carrying that out.

2.3 Coupled case II: b_j is non constant

In this section, we follow Liu and Levin [32], and assume b_j is not a constant: Instead b_j is the function of i_j, such as $b_j \Rightarrow b_j e_j(i_j)$, where

$$e_j(i_j) = \begin{cases} 0 & \text{if } i_j \leq c_j \\ \frac{(i_j - c_j)^3}{(d_j - c_j)^3} & \text{if } c_j < i_j < d_j \\ 1 & \text{if } i_j \geq d_j \end{cases} \tag{2.45}$$

In this section, we consider the one–way coupling case when $e_1(i_1) = 0$,and $e_2(i_2)$ is defined by (2.45).

The equations(2.9) become:

$$\begin{aligned} {i_1}' &= -\mu_1 i_1 - \gamma_1 i_1 + \beta_1 i_1 s_1 + b_2 e_2(i_2) i_2 s_1 \\ {r_1}' &= \gamma_1 i_1 - \mu_1 r_1 - \delta_1 r_1 \qquad (2.46) \\ s_1 + i_1 + r_1 &= 1 \\ {i_2}' &= -\mu_2 i_2 - \gamma_2 i_2 + \beta_2 i_2 s_2 \\ {r_2}' &= \gamma_2 i_2 - \mu_2 r_2 - \delta_2 r_2 \qquad (2.47) \\ s_2 + i_2 + r_2 &= 1. \end{aligned}$$

System (2.47) becomes a single SIR for the pig population independent of the human population with $\delta_2 = 0$ for the pig.

Theorem. System (2.47) has a nontrivial equilibrium(i_2^*, r_2^*), if and only if $\sigma_2 := \frac{\beta_2}{(\mu_2 + \gamma_2)} > 1$. And system (2.46) has a nontrivial equilibrium(i_1^*, r_1^*), if

and only if $\sigma_1 := \frac{\beta_1}{(\mu_1+\gamma_1)} > 1$.

Proof. When $\sigma_2 > 1$, system (2.47) is a single SIRS model which we considered before. When $\sigma_1 > 1$ and $e_2(i_2^*) = 0$, system (2.46) becomes a single SIRS model as well. Hence in this proof, we consider $e_2(i_2^*) \neq 0$. Since $e_2(i_2^*) > 0$, $r_1^* = h_1 i_1^*$ and $s_1^* = 1 - i_1^*/H_1$, where $h_1 = \frac{\gamma_1}{\mu_1}$ (see (2.12) and $H_1 = \frac{1}{1+h_1}$. Also $0 = \beta_1 i_1^* s_1^* - (\mu_1 + \gamma_1) i_1^* + e_2(i_2^*) i_2^* s_1^*$.

We consider the quadratic equation

$$\sigma_1 i_1(1 - i_1/H_1) - i_1 + e(i_2^*) i_2^*(1 - i_1/H_1)/(\mu_1 + \gamma_1) = 0, \qquad (2.48)$$

where $\sigma_1 = \frac{\beta_1}{\mu_1+\gamma_1}$.

The coefficient of the quadratic term is $-\sigma_1/H_1 < 0$ and the constant term is $e(i_2^*) i_2^*/(\mu_1 + \gamma_1) > 0$.

Since these two constants are of different sign it means that this equation has one positive root and one negative root.

Lemma. This positive root ,i_1^*, is smaller than H_1.

Proof. If $i_1^* > H_1$, then $1 - i_1^*/H_1 < 0$. Therefore the leftside of (2.48) is < 0, which is contradiction.

Therefore there exists an unique nontrivial equilibrium.

Theorem. The endemic equilibrium is locally stable when it exists.

Proof. We have the following Jacobian matrix.

$$\mathbf{J} = \begin{pmatrix} -e_2(i_2^*) i_2^* s_1^*/i_1^* - \beta_1 i_1^* - e_2(i_2^*) i_2^* & -\beta_1 i_1^* - e_2(i_2^*) i_2^* & (e_2'(i_2^*) i_2^* + e_2(i_2^*)) s_1^* & 0 \\ \gamma_1 & -\mu_1 - \delta_1 & 0 & 0 \\ 0 & 0 & -\beta_2 i_2^* & -\beta_2 i_2^* \\ 0 & 0 & \gamma_2 & -\mu_2 - \delta_2 \end{pmatrix} \qquad (2.49)$$

To find the eigenvalues of $\mathbf{J}$, we need to consider two block matrices $\mathbf{J_1}, \mathbf{J_2}$, where

$$\mathbf{J_1} = \begin{pmatrix} -e_2(i_2^*)i_2^*s_1^*/i_1^* - \beta_1 i_1^* - e_2(i_2^*)i_2^* & -\beta_1 i_1^* - e_2(i_2^*)i_2^* \\ \gamma_1 & -\mu_1 - \delta_1 \end{pmatrix} \tag{2.50}$$

and,

$$\mathbf{J_2} = \begin{pmatrix} -\beta_2 i_2^* & -\beta_2 i_2^* \\ \gamma_2 & -\mu_2 - \delta_2 \end{pmatrix}. \tag{2.51}$$

Matrices $\mathbf{J_1}$ and $\mathbf{J_2}$ are of the form

$$\mathbf{J_3} = \begin{pmatrix} -a & -b \\ c & -d \end{pmatrix}, \tag{2.52}$$

where $a, b, c, d > 0$.

The characteristic equation corresponding to $\mathbf{J_3}$ looks like

$f(x) = x^2 + (a+d)x + ad + bc = 0$, for each of $\mathbf{J_1}$ and $\mathbf{J_2}$. Since trace $\mathbf{J_3}$ = sum of eigenvalues $= -(a+d) < 0$ and $\det(\mathbf{J_3})$ = product of eigenvalues $= ad + bc > 0$, it implies that all the eigenvalue have negative real part. Therefore the endemic equilibrium is locally stable.

The case when $e_1(i_1) \neq 0, e_2(i_2) \neq 0$ i.e two-way coupling.

We consider two-way coupling numerically. In (2.10), we take $b_j \Rightarrow b_j e_j(i_j)$ where $e_j(i_j)$ is defined in (2.45) We will show numerically that two-way coupling has a periodic solution when b_1 and b_2 are larger than some critical values (see figure 2.4–2.5).

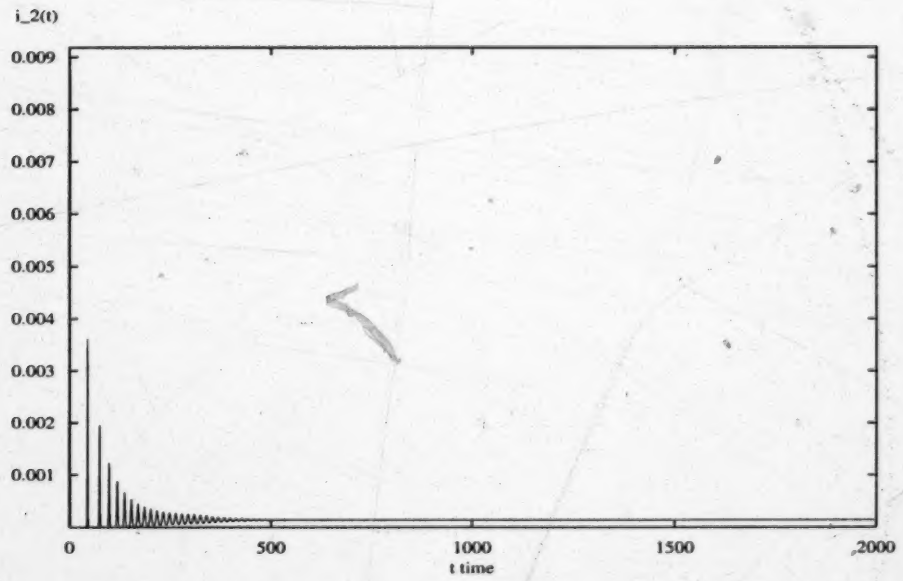


Figure 2.4: There is no periodic solution for two–way coupling case t time vs $i_2(t)$. $b_1 = 0.1$ and $b_2 = 0.3$ see Appendix B for the parameters used in here

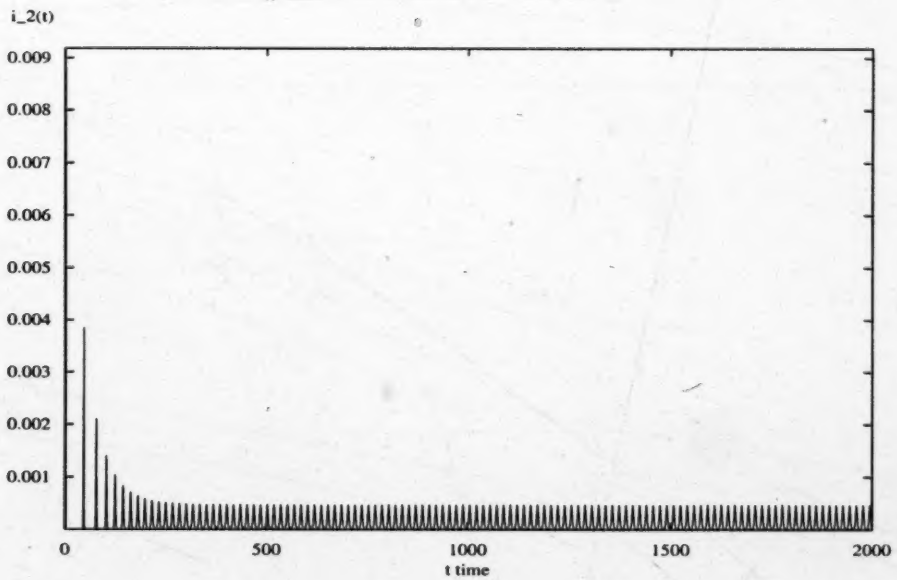


Figure 2.5: Periodic solution for two–way coupling case appears t time vs $i_2(t)$. $b_1 = 0.3$ and $b_2 = 0.3$ see Appendix B for the parameters used in here

$$
\begin{aligned}
i_1{}' &= -\mu_1 i_1 - \gamma_1 i_1 + \beta_1 i_1 s_1 + b_2 e_2(i_2) i_2 s_1 \\
r_1{}' &= \gamma_1 i_1 - \mu_1 r_1 - \delta_1 r_1 \qquad (2.53) \\
s_1 + i_1 + r_1 &= 1 \\
i_2{}' &= -\mu_2 i_2 - \gamma_2 i_2 + \beta_2 i_2 s_2 + b_1 e_1(i_1) i_1 s_2 \\
r_2{}' &= \gamma_2 i_2 - \mu_2 r_2 - \delta_2 r_2 \qquad (2.54) \\
s_2 + i_2 + r_2 &= 1,
\end{aligned}
$$

where function e_j is defined as (2.45).

Using XPP (see Appendix B), we demonstrate the existence of the periodic solutions of (2.53)–(2.54).

From figure 2.6 to figure 2.8 and figure 2.9 to figure 2.11, we can see that as b_1 and b_2 increase, the length of the period becomes longer and the rate of infection becomes higher.

symbol	value	symbol	value
β_1	37.66	β_2	40.0
μ_1	0.004	μ_2	0.0028
γ_1	33.333	γ_2	33.333
δ_1	0.01	δ_2	0.0
c_1	0.00008	c_2	0.0002
d_1	0.0001	d_2	0.00022

Table 2.1: Data of the two–way coupling with varying b_j for $j = 1, 2$.

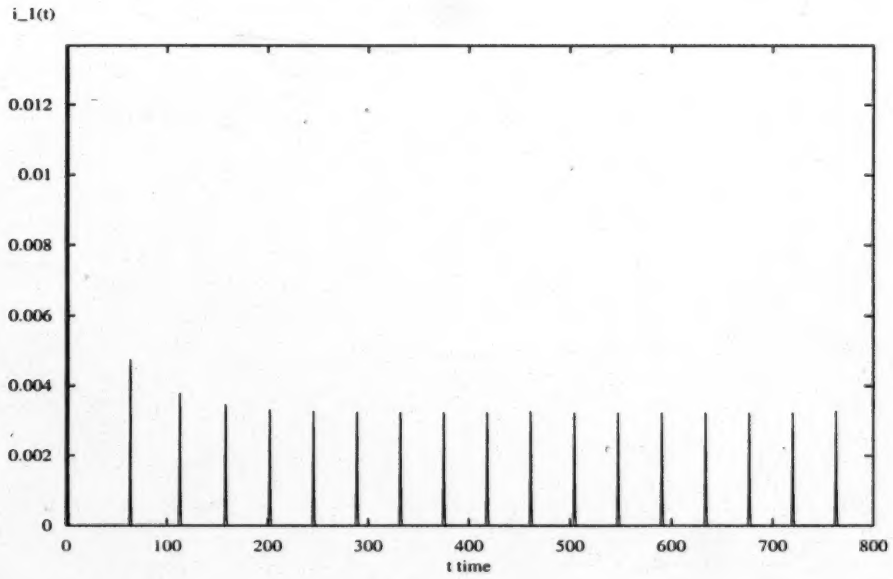


Figure 2.6: Periodic solution for the two–way coupling case t time vs $i_1(t)$. $b_1 = 2.0$ and $b_2 = 2.5$. See table 2.1 for the other parameters used in here.

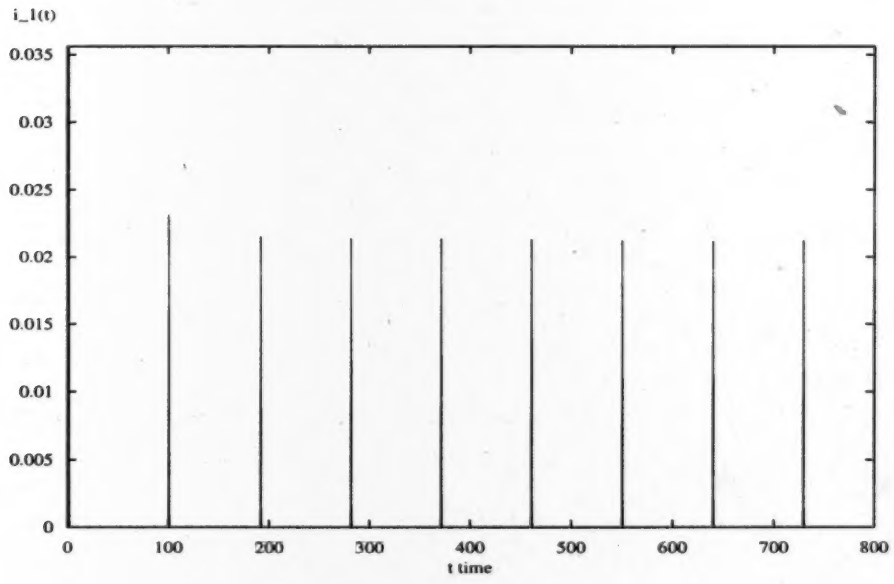


Figure 2.7: Periodic solution for the two–way coupling case t time vs $i_1(t)$. $b_1 = 7.0$ and $b_2 = 8.0$. See 2.1 for the other parameters used in here.

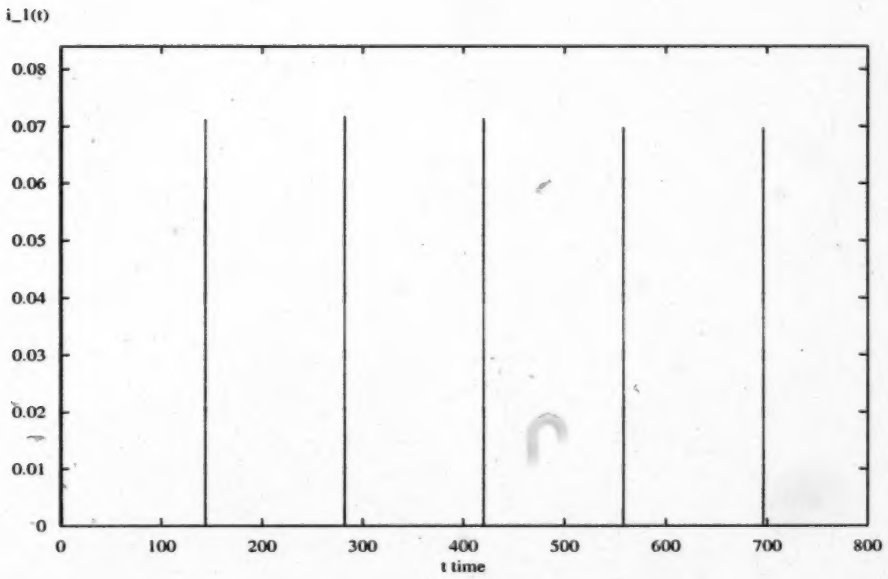


Figure 2.8: Periodic solution for the two–way coupling case t time vs $i_1(t)$. $b_1 = 17.0$ and $b_2 = 18.0$. See 2.1 for the other parameters used in here.

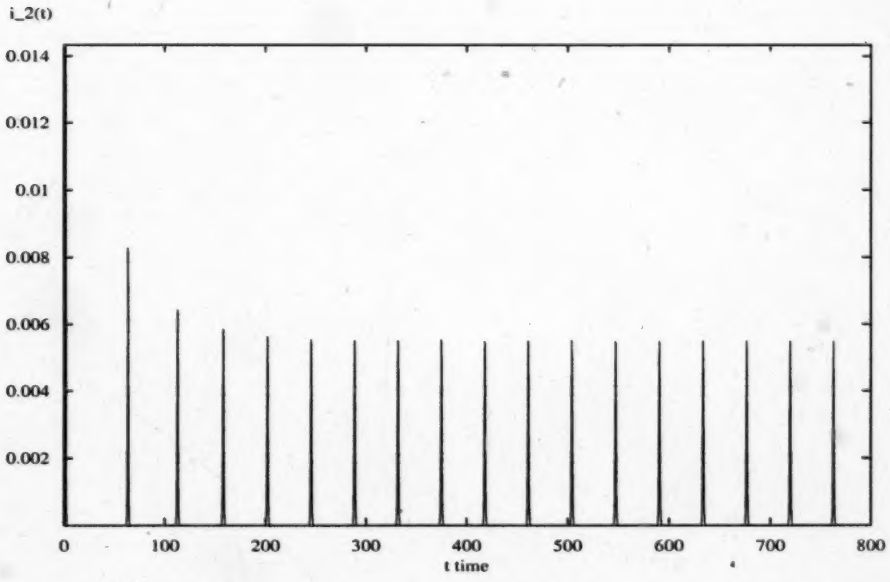


Figure 2.9: Periodic solution for the two–way coupling case t time vs $i_2(t)$. $b_1 = 2.0$ and $b_2 = 2.5$. See 2.1 for the other parameters used in here.

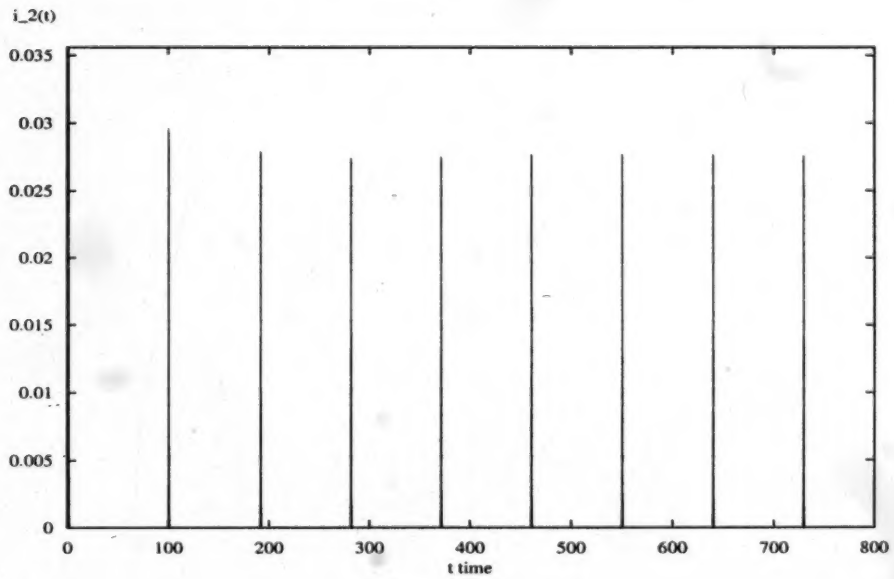


Figure 2.10: Periodic solution for the two–way coupling case t time vs $i_2(t)$. $b_1 = 7.0$ and $b_2 = 8.0$. See 2.1 for the other parameters used in here.

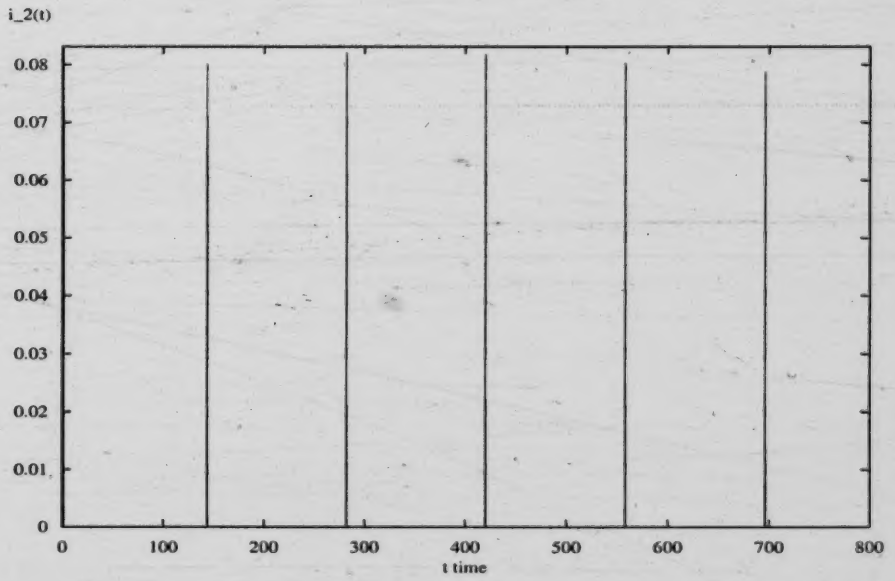


Figure 2.11: Periodic solution for the two–way coupling case t time vs $i_2(t)$. $b_1 = 17.0$ and $b_2 = 18.0$. See 2.1 for the other parameters used in here.

2.4 Discussion and numerical results

DDE23(matlab base)[46] (see Appendix B) is now used to verify that there is no periodic solution in the two hosts SIRS model with no time delay.

Figure(2.12) to Figure(2.17) show i vs r phase portrait as μ_1 and μ_2 (see the diagram(1.1)) change. There does not appear any periodic solution.

symbol	value	symbol	value
β_1	0.1	β_2	0.2
γ_1	0.02	γ_2	0.05
δ_1	0.0033	δ_2	0.0
b_1	0.01	b_2	0.01

Table 2.2: Data of two SIRS system with varying μ_j for $j = 1, 2$.

Figure(2.18) to Figure(2.25) show i vs r phase portrait as b_1 and b_2 (see the diagram(1.1)) change. There does not appear to be any periodic solution as well. The numerical evidence points to the conjecture that the endemic equilibrium is globally stable when it exists for the case b_1, b_2 are constant.

symbol	value	symbol	value
β_1	0.1	β_2	0.2
μ_1	0.000004	μ_2	0.004
γ_1	0.02	γ_2	0.05
δ_1	0.0033	δ_2	0.0

Table 2.3: Data of two SIRS system with varying b_j for $j = 1, 2$.

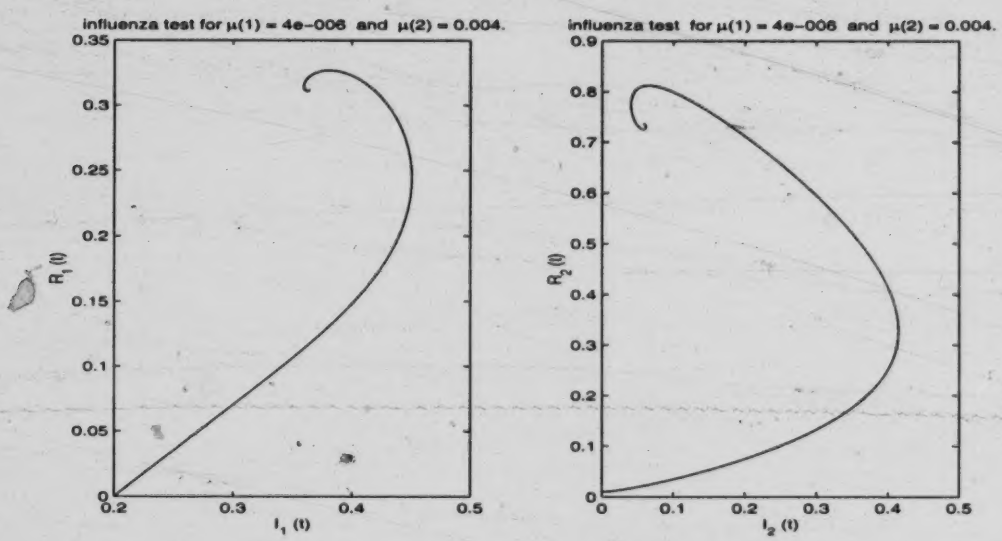


Figure 2.12: $i - r$ plane of two hosts cross infection with no time delay term for $\mu_1 = 4e - 006$ and $\mu_2 = 0.004$.

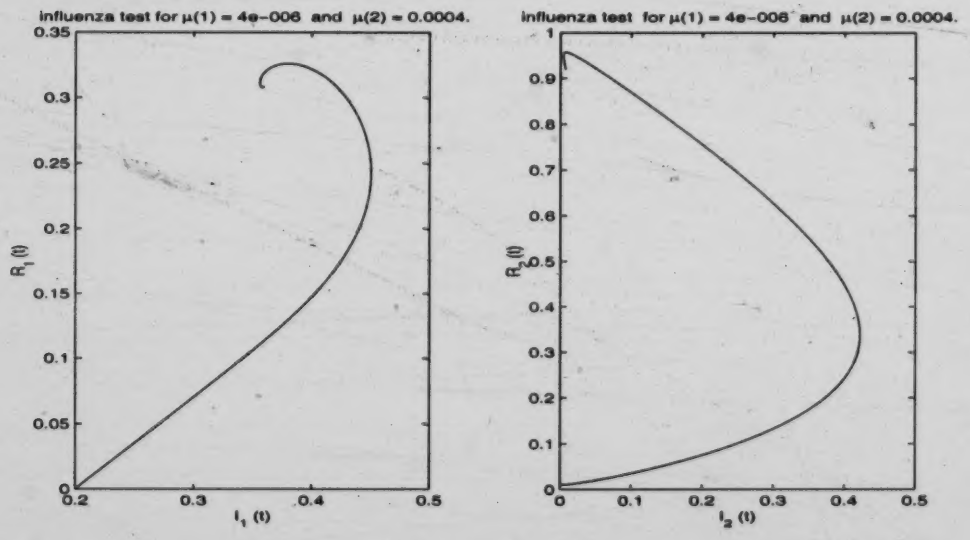


Figure 2.13: $i - r$ plane of two hosts cross infection with no time delay term for $\mu_1 = 4e - 006$ and $\mu_2 = 0.0004$.

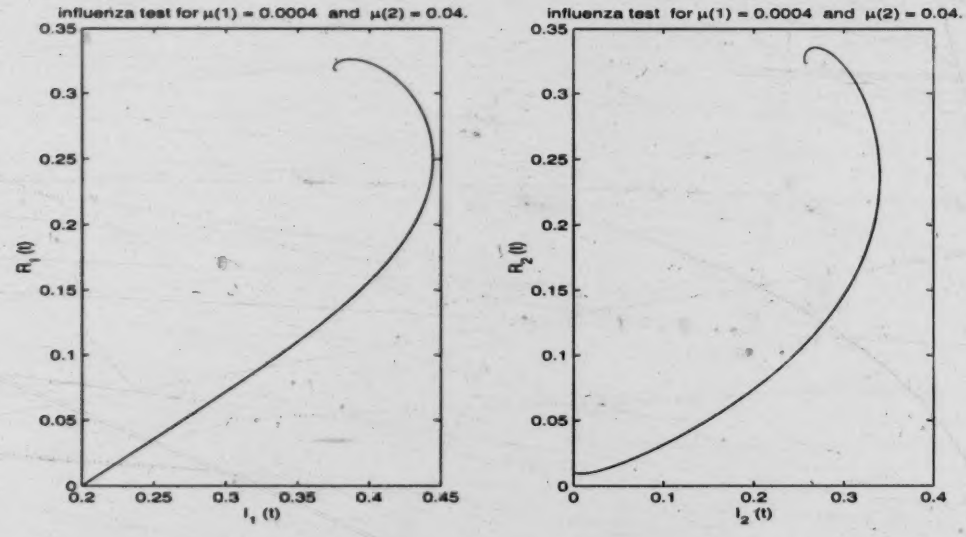


Figure 2.14: $i - r$ plane of two hosts cross infection with no time delay term for $\mu_1 = 0.0004$ and $\mu_2 = 0.04$.

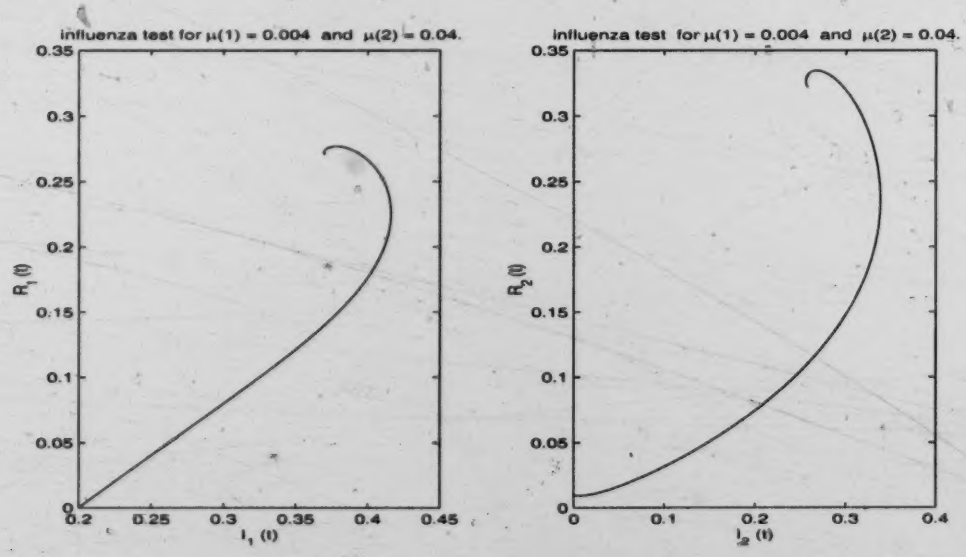


Figure 2.15: $i - r$ plane of two hosts cross infection with no time delay term for $\mu_1 = 0.004$ and $\mu_2 = 0.04$.

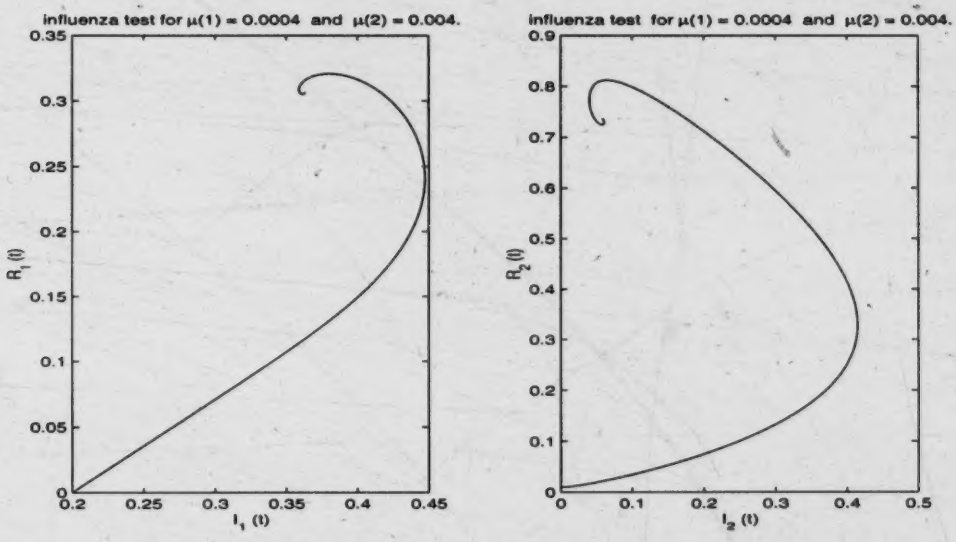


Figure 2.16: $i - r$ plane of two hosts cross infection with no time delay term for $\mu_1 = 0.0004$ and $\mu_2 = 0.004$.

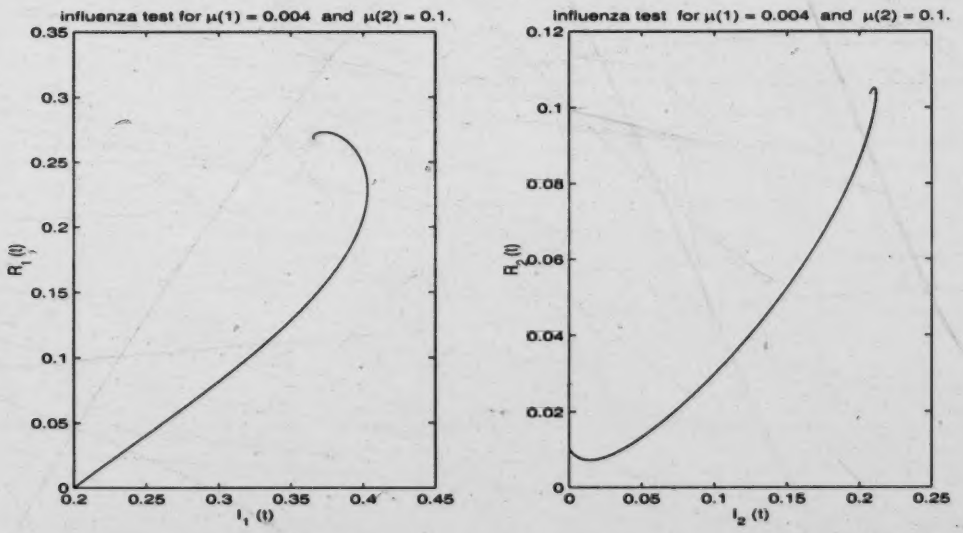


Figure 2.17: $i - r$ plane of two hosts cross infection with no time delay term for $\mu_1 = 0.004$ and $\mu_2 = 0.1$.

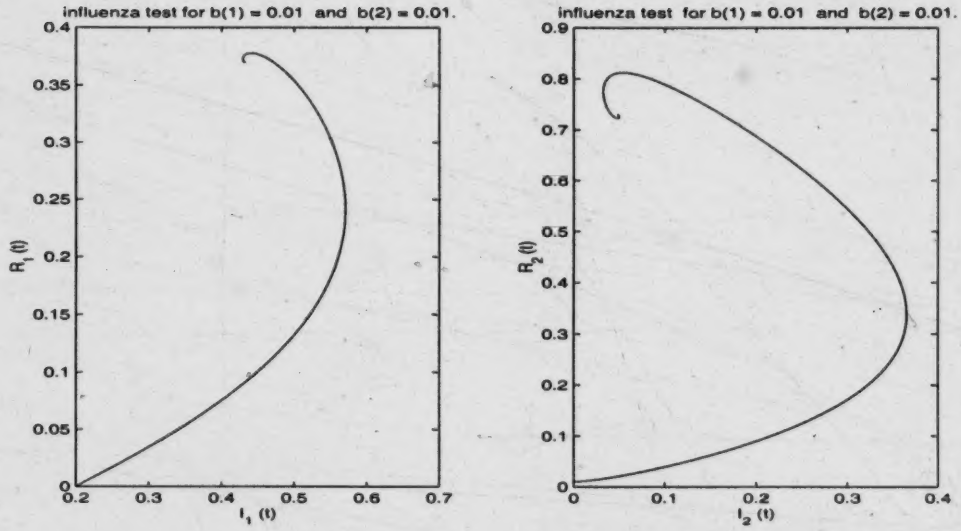


Figure 2.18: $i - r$ plane of two hosts cross infection with no time delay term for $b_1 = 0.01$ and $b_2 = 0.01$.

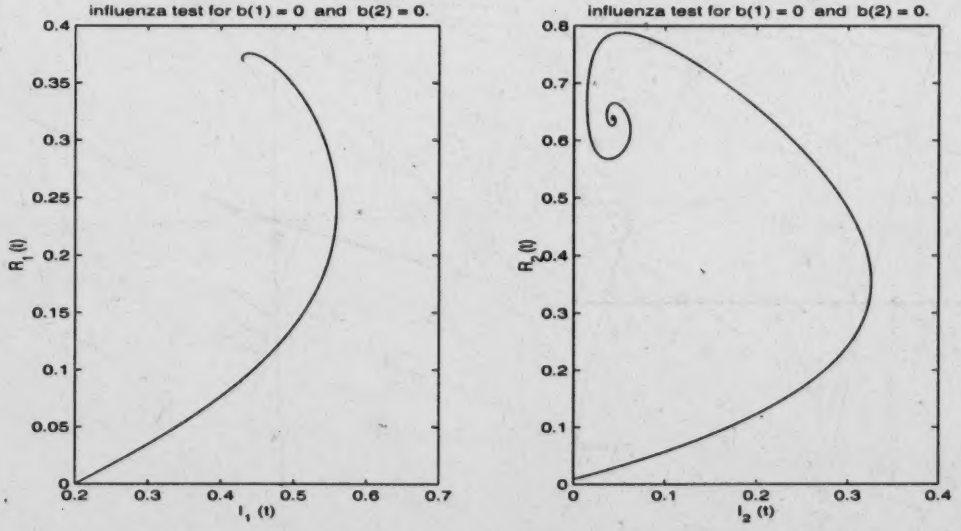


Figure 2.19: $i - r$ plane of two hosts cross infection with no time delay term for $b_1 = 0.0$ and $b_2 = 0.0$.

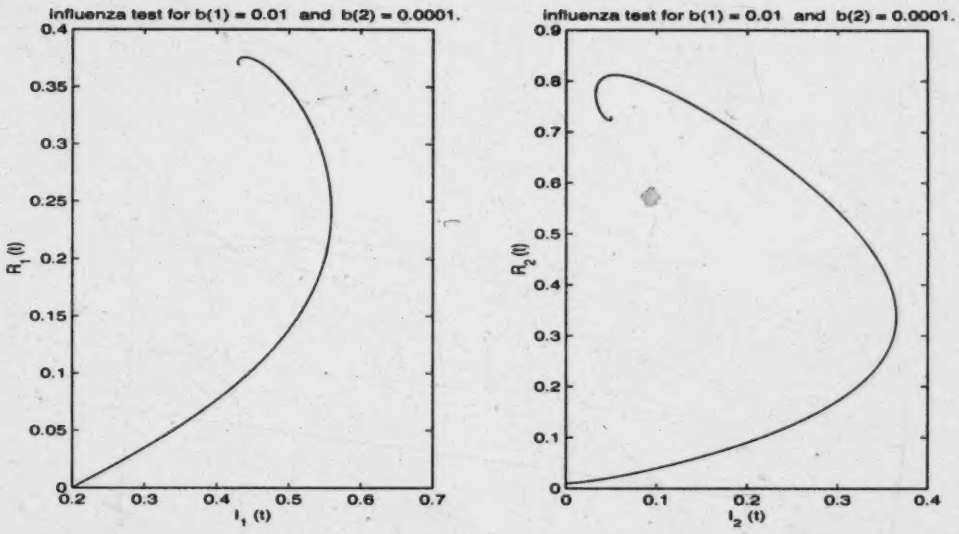


Figure 2.20: $i - r$ plane of two hosts cross infection with no time delay term for $b_1 = 0.01$ and $b_2 = 0.0001$.

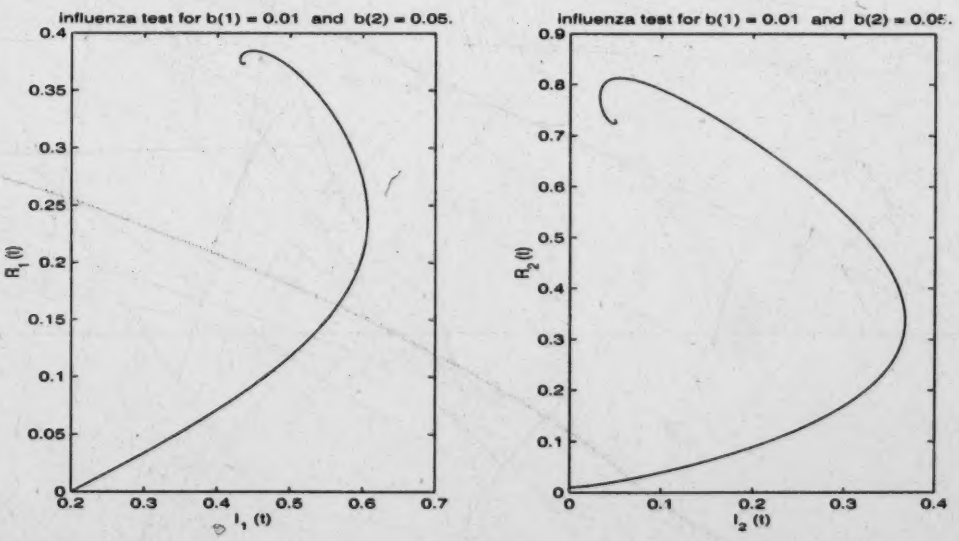


Figure 2.21: $i - r$ plane of two hosts cross infection with no time delay term for $b_1 = 0.01$ and $b_2 = 0.05$.

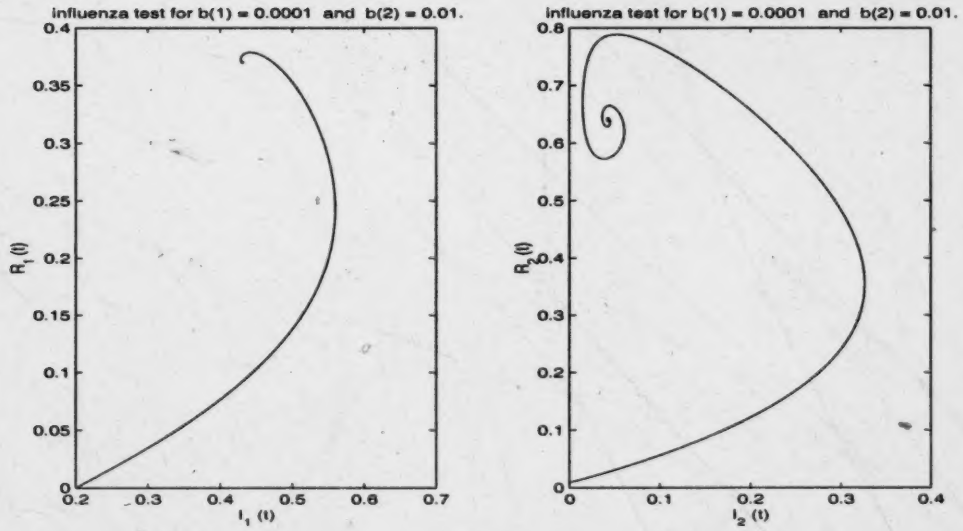


Figure 2.22: $i - r$ plane of two hosts cross infection with no time delay term for $b_1 = 0.0001$ and $b_2 = 0.01$.

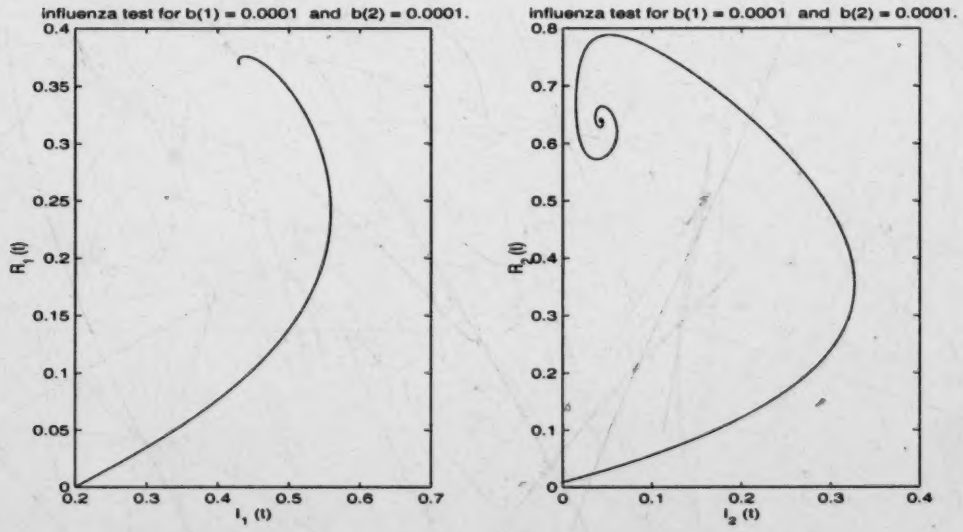


Figure 2.23: $i - r$ plane of two hosts cross infection with no time delay term for $b_1 = 0.0001$ and $b_2 = 0.0001$.

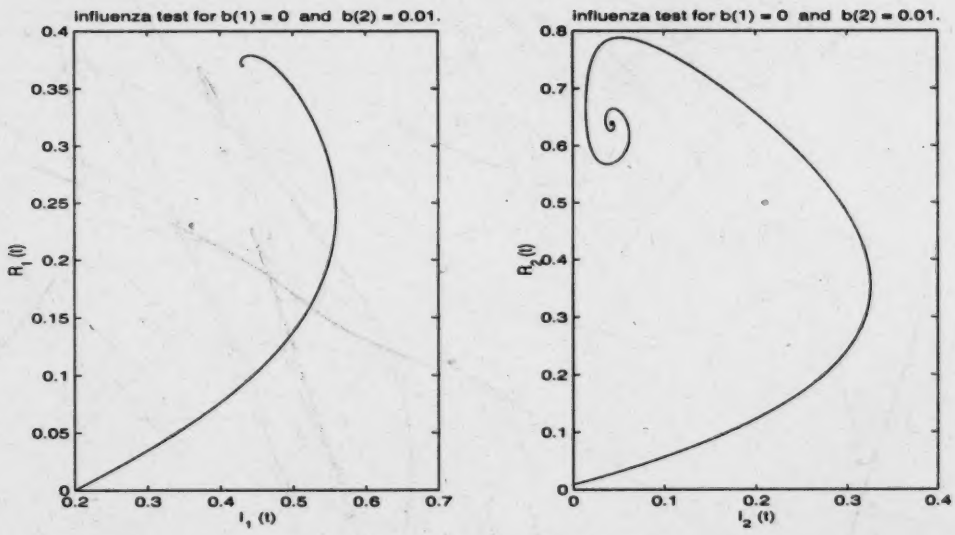


Figure 2.24: $i - r$ plane of two hosts cross infection with no time delay term for $b_1 = 0.0$ and $b_2 = 0.01$.

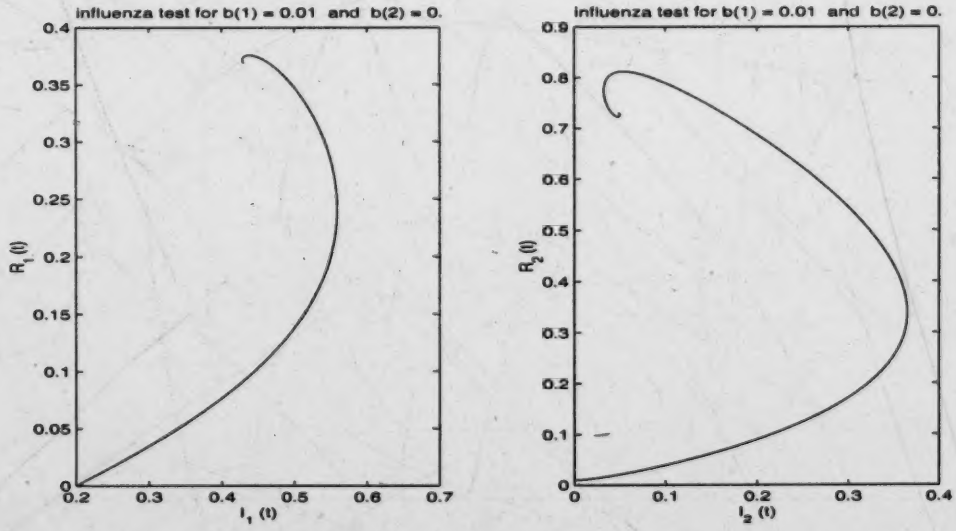


Figure 2.25: $i - r$ plane of two hosts cross infection with no time delay term for $b_1 = 0.01$ and $b_2 = 0.0$.

2.5 Conclusion

In this Chapter, we show that SIRS model without cross infection has globally stable endemic equilibrium for $\sigma := \beta/(\mu+\gamma) > 1$. When there is cross infection, we show that coupled SIRS with constant b_j has endemic equilibrium for $(1-\sigma_1)(1-\sigma_2) < \frac{b_1 b_2}{(\gamma_1+\mu_1)(\gamma_2+\mu_2)}$, which includes case $\sigma_1 > 1$ or $\sigma_2 > 1$. Because of b_j, there occurs endemic equilibrium even though $\sigma_1 < 1$ and $\sigma_2 < 1$, which means that cross infection gives virius more chance to survive or sustain with less antigenic shift or drift. We show that disease–free equilibrium is locally and globally stable with some condition without endemic equilibrium. And we find that endemic equilibrium is locally stable for symmetric case, but we could not show fully the local stability of endemic equilibrium generally. We use numerically to show that. From numerical simulation, we could see that there is no periodic solution for constant b_j. However, we could see that there appears periodic solution when we use non–constant b_j.

Chapter 3

Model with Delay

Hethcote, Stech and van den Driessche [22] showed that periodic solution can exist in SIRS model with time delay even when vital dynamics was not included. Hethcote, Lewis and van den Driessche [21] showed that there appears periodic solutions for some parameter values in SIRS delay model with a nonlinear incidence rate. Hethcote and van den Driessche [23] mentioned periodic solutions in SIRS delay model with vital dynamics. However the detailed algebraic and numerical calculations related to Hopf bifurcation were not carried out for their model [23].

In this chapter, we will try to do the detailed algebraic and numerical calculations with several tools for a single SIRS model with time delay and a coupled SIRS model with one time delay as well.

3.1 Single host SIRS with one delay term

In this chapter, we use the fact that human population lives longer than the time period of temporary immunity, namely τ, so that there is one time delay for human. On the contrary, pig does not survive longer than the time period

of temporary immunity due to being slaughtered, therefore we do not need a time delay for the pig population. Without a time delay, the model of the pig population is expressed as the second part of 2.10. For the part of the human population, we assume that before time passes τ, no individual comes back into s (susceptible class) and, each individual starts to comes out of r (recovered class) (into s) (susceptible class) τ units after entering r (recovered class), which is expressed as $\gamma i(t-\tau)$, except that some die in r (recovered class). Let $g := \gamma i(t-\tau)$, then we can see that $g' = -\mu g$. Solving this differential equation from 0 to τ, $g(\tau) = g(0)\exp(-\mu\tau)$. Hence the rate of coming out of r, τ units after entering r, is $g(0)\exp(-\mu\tau) = \gamma i(t-\tau)\exp(-\mu\tau)$. Therefore r need to be divided by two cases (for $t \leq \tau$ and $t > \tau$).

Then the dynamical model is written as:

$$
\begin{aligned}
{i_1}' &= -\mu_1 i_1 - \gamma_1 i_1 + \beta_1(1-i_1-r_1)i_1 + b_2(1-i_1-r_1)i_2 \\
{r_1}' &= \begin{cases} \gamma_1 i_1 - \mu_1 r_1 & \text{if } t \leq \tau \\ \gamma_1 i_1 - \mu_1 r_1 - \gamma_1 \exp(-\mu_1\tau) i_1(t-\tau) & \text{otherwise} \end{cases} \\
{i_2}' &= -\mu_2 i_2 - \gamma_2 i_2 + \beta_2(1-i_2-r_2)i_2 + b_1(1-i_2-r_2)i_1 \\
{r_2}' &= \gamma_2 i_2 - \mu_2 r_2.
\end{aligned}
\tag{3.1}
$$

In this equations (3.1) (see [22, 21, 23], τ is delay term and the other parameters are the same as in chapter2. Because human has long life cycle compared to temporary immunity, human group has delay term here. On the contrary, pig group does not have a delay term owing to their short life cycle (within one year). First we consider the human group with a delay term. It is modelled by equation (3.2). Later the full equation (3.1) is considered using numerical simulation.

$$
\begin{aligned}
i'(t) &= \beta i(t)s(t) - (\mu+\gamma)i(t) \\
r'(t) &= \begin{cases} \gamma i(t) - \mu r(t) & \text{if } t \le \tau \\ \gamma i(t) - \mu r(t) - \gamma \exp(-\mu\tau) i(t-\tau) & \text{if } t > \tau, \end{cases}
\end{aligned} \tag{3.2}
$$

where $s = 1 - (i + r)$.

The positive equilibrium (i^*, r^*) for (3.2) satisfies

$$\beta i^*(1 - i^* - r^*) - (\mu+\gamma)i^* = 0. \tag{3.3}$$

Divide by i^*, we have

$$\beta(1 - i^* - r^*) = (\mu+\gamma), \tag{3.4}$$

so that

$$r^* = 1 - (\mu+\gamma)/\beta - i^*. \tag{3.5}$$

Using the second equation in (3.2), we have

$$\gamma i^* - \gamma \exp(-\mu\tau) i^* = \mu r^*, \tag{3.6}$$

or

$$\gamma(1 - \exp(-\mu\tau))i^* = \mu r^* = \mu(1 - (\mu+\gamma)/\beta - i^*) \tag{3.7}$$

so that

$$i^* = \frac{\mu(\beta - (\mu+\gamma))}{\beta(\gamma(1 - e^{-\mu\tau}) + \mu)} > 0, \text{ for } \beta > \mu+\gamma \tag{3.8}$$

and

$$
\begin{aligned}
r^* &= (\beta - (\mu+\gamma))/\beta - i^* \\
&= (1 - \frac{\mu+\gamma}{\beta}) \left[\frac{\gamma(1 - e^{-\mu\tau})}{\gamma(1 - e^{-\mu\tau}) + \mu} \right] \\
&> 0, \text{ for } \beta > \mu+\gamma.
\end{aligned} \tag{3.9}
$$

THus we see that the positive equilibrium exists if and only if $\beta > \mu + \gamma$. Let us linearize equation (3.2) about (i^*, r^*)

Set

$$\bar{i} = i - i^* \tag{3.10}$$

$$\bar{r} = r - r^*. \tag{3.11}$$

Then

$$\begin{aligned} \bar{i}' &= \beta i(1 - i - r) - (\mu + \gamma)i \\ &= \beta(\bar{i} + i^*)(1 - (\bar{i} + \bar{r}) - (i^* + r^*)) - (\mu + \gamma)(\bar{i} + i^*) \\ &= \beta\bar{i}(1 - (\bar{i} + \bar{r}) - (i^* + r^*)) - \beta i^*(\bar{i} + \bar{r}) - (\mu + \gamma)\bar{i}, \end{aligned} \tag{3.12}$$

since $\beta i^*(1 - (i^* + r^*)) - (\mu + \gamma)i^* = 0$. So up to linear term we have

$$\bar{i}' = (\beta - (\mu + \gamma) - 2\beta i^* - \beta r^*)\bar{i} - \beta i^* \bar{r}.$$

We can take the same steps for r. Then for $t > \tau$

$$\begin{aligned} \bar{r}' &= \gamma i - \mu r - \gamma \exp(-\mu\tau) i(t - \tau) \\ &= \gamma\bar{i} - \mu\bar{r} - \gamma \exp(-\mu\tau)\bar{i}(t - \tau) + \gamma i^* - \mu r^* - \gamma \exp(-\mu\tau) i^* \\ &= \gamma\bar{i} - \mu\bar{r} - \gamma \exp(-\mu\tau)\bar{i}(t - \tau), \end{aligned} \tag{3.13}$$

by (3.6)

From now on, we replace $\bar{i}$ by i and $\bar{r}$ by r for simplicity of notation and we obtain the linearized equation for (3.6) as

$$i' = (\beta - (\mu + \gamma) - 2\beta i^* - \beta r^*)i - \beta i^* r. \tag{3.14}$$

$$r' = \gamma i - \mu r - \gamma \exp(-\mu\tau) i(t - \tau). \tag{3.15}$$

Let

$$a = (\beta - (\mu + \gamma) - 2\beta i^* - \beta r^*),$$
$$b = -\beta i^*,$$
$$c = \gamma,$$
$$d = -\mu,$$
$$f = -\gamma \exp(-\mu\tau).$$

Then $a = b < 0$, $c > 0$, $d < 0$ and $f < 0$, by (3.4)

To find the characteristic equation for (3.14)–(3.15), we plug the trial solution $i(t) = X_0 \exp(\xi t)$, and $r(t) = Y_0 \exp(\xi t)$ into (3.14)–(3.15), where X_0 and Y_0 are not both zero.

After dividing by $\exp(\xi t)$, we get

$$X_0\xi = aX_0 + bY_0 \tag{3.16}$$
$$Y_0\xi = cX_0 + dY_0 + fX_0 \exp(-\xi\tau). \tag{3.17}$$

Since X_0 and Y_0 are not both zero, the coefficient matrix should be nonsingular that is, $\det(\mathbf{J}) \neq 0$ where

$$\mathbf{J} = \begin{pmatrix} \xi - a & -b \\ -c - f\exp(-\xi\tau) & \xi - d \end{pmatrix}. \tag{3.18}$$

The condition $\det(\mathbf{J}) = 0$ gives us the characteristic equation.

$$(\xi - a)(\xi - d) - b(c + f\exp(-\xi\tau)) = 0 \tag{3.19}$$

and ξ is a characteristic root here.

Claim. $\xi = 0$ cannot be a characteristic root.

Proof of Claim. Plug $\xi = 0$ into the equation (3.19), we need $ad = b(c+f)$. Now since $a < 0,\ d < 0,\ b < 0,\ c+f > 0$, therefore the left hand side is positive and the right hand side is zero. Hence $\xi = 0$ cannot be a root of (3.19).

Theorem. (3.19) can have purely imaginary roots.

Proof. Plug $\xi = i\lambda$ $(\lambda > 0)$ into the equation(3.19). Then

$$(ad - bc) - \lambda^2 = bf\cos(\lambda\tau) \tag{3.20}$$

$$(a+d)\lambda = bf\sin(\lambda\tau). \tag{3.21}$$

We need to see if we can solve for $\lambda > 0,\ \tau > 0$.

Square both sides of (3.20)–(3.21) and add them, we have

$$\{(ad - bc) - \lambda^2\}^2 + \{(a+d)\lambda\}^2 = b^2f^2. \tag{3.22}$$

Let $\lambda^2 = T > 0$. Then we have

$$\{(ad - bc) - T\}^2 + (a+d)^2T = b^2f^2. \tag{3.23}$$

Rearrange (3.23) in decreasing order of T, we have

$$T^2 + (a^2 - 2bc + d^2)T + (ad - bc)^2 - b^2f^2 = 0. \tag{3.24}$$

Claim. (3.24) can have two positive solutions.

Proof of Claim. Since (3.24) is quadratic equation, the standard form of (3.24) is (3.26).

Because $C = a^2\{(d-c)^2 - f^2\} > 0$, two roots of (3.24) should be same sign. In

order to have positive real roots, (3.24) should satisfy following two conditions. (1) $B < 0$ and (2) $B^2 - 4C \geq 0$ discriminant should be non–negative.
Since $a = b$ from (3.4),(3.24) can be written as

$$T^2 - (2a(d-c) - (a+d)^2)T + a^2\{(d-c)^2 - f^2\} = 0. \tag{3.25}$$

Since d is negative , c is positive, and $c^2 > f^2$, the constant term is positive. the first condition is satisfied. Here $C = a^2\{(d-c)^2 - f^2\} > 0$ and $B = (a+d)^2 - 2a(d-c)$. Then (3.24) becomes

$$T^2 + BT + C = 0 \tag{3.26}$$

Next, we need to check the second condition ($B < 0$). $B = \mu/(\gamma - \gamma\exp(\mu\tau) + \mu)^2 A$, where

$$\begin{aligned} A = &-2\lambda\gamma^2 + 2\lambda\gamma^2\exp(-\mu\tau) - 4\gamma\lambda\mu + \sigma\mu\gamma^2 - 4\mu\gamma^2\exp(-\mu\tau) \\ &+ 6\gamma\mu^2 + 2\gamma^3 - 2\gamma^3\exp(-\mu\tau) + \mu\lambda^2 - 2\lambda\mu^2 + 2\mu^3 \\ &+ \mu\gamma^2\exp(-2\mu\tau) - 2\mu^2\gamma\exp(-\mu\tau) \end{aligned} \tag{3.27}$$

Note that A and B have the same sign here.

Let $\alpha = \lambda - (\mu + \gamma)$. Then $\alpha > 0$.
We will consider A as a function of α as follows

$$\begin{aligned} A(\alpha) = &\mu\gamma^2\exp(-2\mu\tau) - 2\mu^2\gamma\exp(-\mu\tau) - 2\mu\gamma^2\exp(-\mu\tau) + \mu\gamma + 2\gamma\mu^2 - 2\gamma^2\alpha \\ &+ \mu^3 + \mu\alpha - 2\mu\gamma\alpha + 2\gamma^2\exp(-\mu\tau)\alpha. \end{aligned} \tag{3.28}$$

$$\begin{aligned} A(0) &= \mu\gamma^2\exp(-2\mu\tau) - 2\mu^2\gamma\exp(-\mu\tau) - 2\mu\gamma^2\exp(-\mu\tau) + \mu\gamma + 2\gamma\mu^2 + \mu^3 \\ &= \mu\gamma^2(\exp(-2\mu\tau) + 1 - 2\exp(-\mu\tau)) + 2\gamma\mu^2(1 - \exp(-\mu\tau)) + \mu^3 > 0. \end{aligned} \tag{3.29}$$

Note that $A(0)$ is positive, because $\mu > 0, \quad 1 \geq \exp(-\mu\tau)$
and $\exp(-2\mu\tau) + 1 - 2\exp(-\mu\tau) = \{\exp(-\mu\tau) - 1\}^2 \geq 0$.

B should be negative. It implies that $A(\alpha)$ should be negative as well.
$A(\alpha) = \mu\alpha^2 - 2\gamma(\mu + \gamma - \gamma\exp(-\mu\tau))\alpha + A(0)$.
This equation is a quadratic equation, which has condition $\mu > 0, A(0) > 0$. When the discriminant is positive, $A(\alpha)$ has negative part since it has two distinct positive.
Let $F(\alpha) = (\gamma(\mu + \gamma - \gamma\exp(-\mu\tau)))^2 - \mu A(0) > 0$ (discriminant of $A(\alpha)$),
$F(\alpha) = 4(\gamma - \mu)(\gamma + \mu)(\mu^2 + 2\mu\gamma^2\mu\gamma\exp(-\mu\tau) - 2\gamma^2\exp(-\mu\tau) + \gamma^2\exp(-2\mu\tau) + \gamma^2)$,
since $\mu > 0, \ \gamma > 0, \ \gamma \geq \mu$. To check the sign of $F(\alpha)$, we need to check the sign of
$G(\alpha) = (\mu^2 + 2\mu\gamma^2\mu\gamma\exp(-\mu\tau) - 2\gamma^2\exp(-\mu\tau) + \gamma^2\exp(-2\mu\tau) + \gamma^2)$,

since $\mu\gamma > \mu\gamma\exp(-\mu\gamma), \exp(-2\mu\tau) - 2\exp(-\mu\tau) + 1 = \{\exp(-\mu\tau) - 1\}^2 > 0$
For all $\alpha > 0, G(\alpha) > 0$. Therefore $F(\alpha) > 0$.
It means that there exists α such that $A(\alpha) < 0$.
Finally we need to check the third condition ($B^2 - 4C \geq 0$ i.e. discriminant is non–negative).

$$D := B^2 - 4C = a^4 - 2a^2d^2 + 4a^3c + d^4 + 4d^2ac + 8a^2dc + 4f^2. \qquad (3.30)$$

Similarly we can make D function of α with let $\alpha = \lambda - (\mu + \gamma)$. Then we see that denominator of $D(\alpha)$ is always positive and numerator of $D(\alpha)$ become degree 3 polynomial of α. The leading term (coefficient of α^3) is $4\gamma^2\mu^3\exp(-\mu\tau) - 4\gamma^2\mu^3 - 4\gamma\mu^4 < 0$. The constant term is function of μ, τ and γ. When we collect this constant term with respect to γ, we have degree 6 polynomial. The coefficient of γ is $-4\mu^7\exp(-\mu\tau) + 4\mu^7 > 0$ and constant term is μ^8. Therefore for

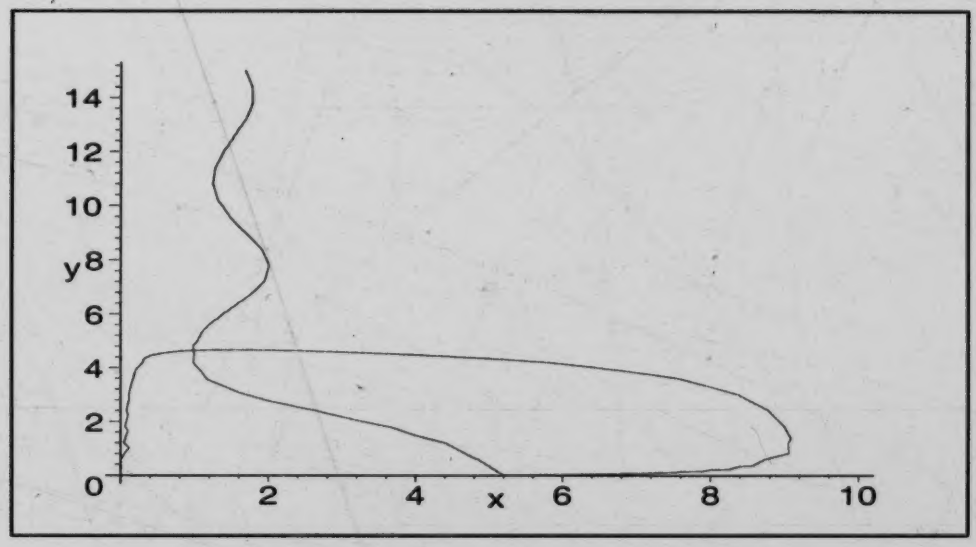


Figure 3.1: One periodic solution as γ changes. $x = \gamma$ and $y = \lambda^2 = T > 0$, $\mu = 0.004$, $\lambda = 10$ and $\tau := 3$. .

small γ the constant term of D becomes positive, and we can find some α such that D is non–negative. Specially when $\gamma = \mu$, we see that constant term of D is $16\mu^8 + 64\mu^6 * \exp(-2\mu\tau) - 8\mu^8 \exp(-3\mu\tau) - 128\mu^6 \exp(-3\mu\tau) + 24\mu^8 \exp(-2\mu\tau) + \mu^8 \exp(-4\mu\tau) + 96\mu^6 \exp(-4\mu\tau) - 32\mu^6 \exp(-5\mu\tau) - 32\mu^8 \exp(-\mu\tau) + 4\mu^6 \exp(-6\mu\tau,$ which is computed to be positive.

Therefore for α, μ, τ and γ which satisfy both $A(\alpha) < 0$ and $D >$, *Claim* is proven here. Therefore Theorem is proven as well.

(3.26) has two positive roots.

Using Maple, we can see that Figure (3.1) shows that there may be one periodic solution as γ changes and other parameters are fixed in .

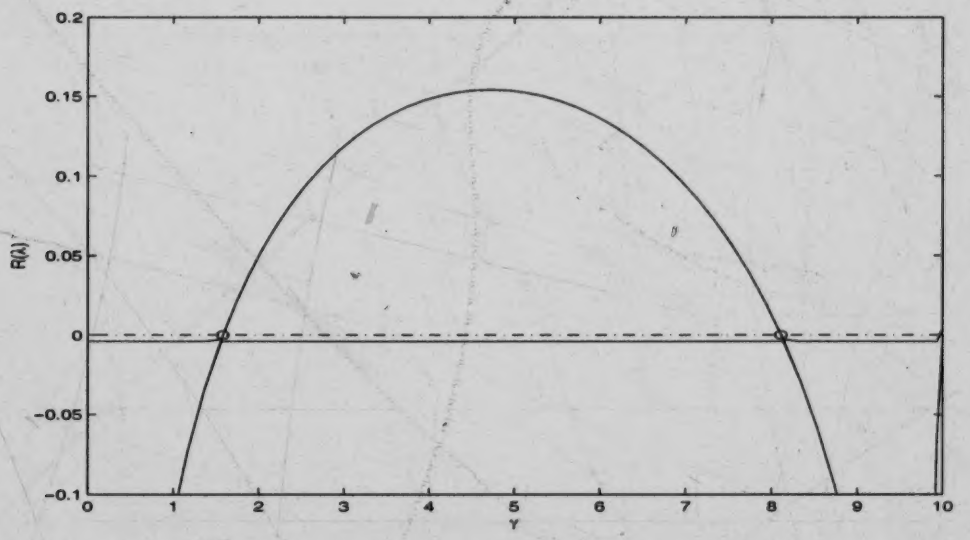


Figure 3.2: The real parts of the rightmost roots of the characteristic equation for $\beta = 10$, $\tau = 3$, $\mu = 0.004$, $\gamma \in [0, 10]$. Hopf bifurcations are indicated with a 'o'.

3.2 Discussion and numerical results

(I). Using DDEBIF [10, 11] (see Appendix B), we computed the real part of the rightmost roots of the characteristic equation of the endemic steady state solution of 3.2 as γ change.

Time is rescaled to $100\times$ and other parameters are rescaled to $1/100\times$.

(II). We use Campbell's Maple program(cm.gen) to calculate the reduced equation on the centre manifold for the delay equations(3.2) (see Appendix B). The coefficients of the reduced equation on the center manifold are calculated. Campbell's other Maple program (nf.gen) finds the coefficients of the Takens normal form for the reduced equation. Among them, $a11$ determines the stability of the bifurcated periodic orbit. $a11 < 0$ means it is a stable bifurcated periodic orbit. It turns out for (3.12) $a11 = 0$. Therefore to determine the stability of

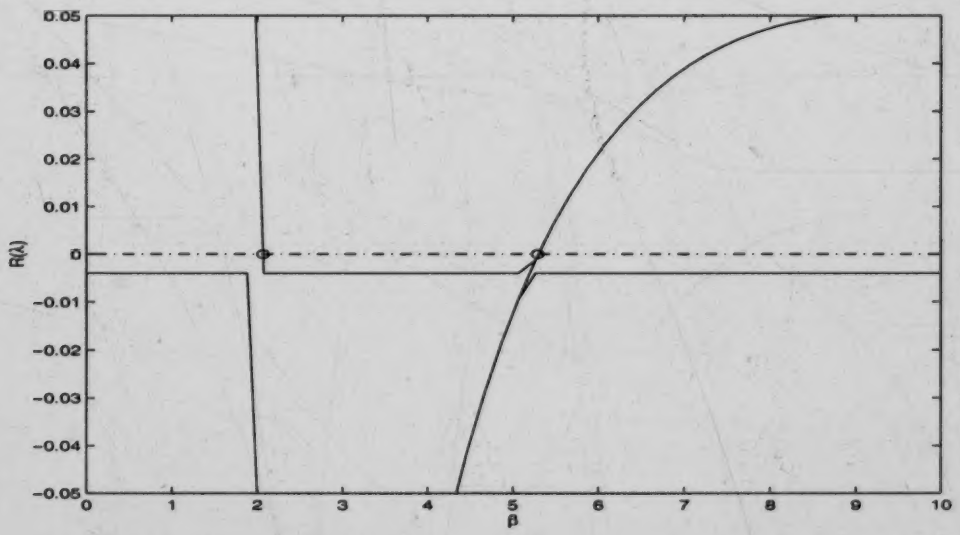


Figure 3.3: The real parts of the rightmost roots of the characteristic equation for $\gamma = 2$, $\tau = 3$, $\mu = 0.004$, $\beta \in [0, 10]$. Hopf bifurcations are indicated with a 'o'.

bifurcated periodic orbit, we need to go to fifth order terms. We have not carried that out for this thesis.

(III). DDE23(matlab base)[46] (see Appendix B) is used to show numerically that there is a periodic solution in the two hosts SIRS model with one time delay.

Figure(3.4) to Figure(3.11) show i vs r graphs as the b_1 and b_2 (see the diagram(1.1) change. There appears periodic solution. When the b_1 and b_2 are zero, there is periodic solution in the first host and not in the second host. In those figures, one sees that there appears periodic solution in the second host as b_1 and b_2 change. As cross infection becomes stronger, the periodic solution in first group shrinks and one in the second group swells. The b_1 (more than b_1) plays a role to make second periodic solution appear in the second group.

symbol	value	symbol	value
β_1	0.1	β_2	0.2
μ_1	0.000004	μ_2	0.004
γ_1	0.02	γ_2	0.05
τ	300		

Table 3.1: Data of two SIRS system with varying b_j for $j = 1, 2$.

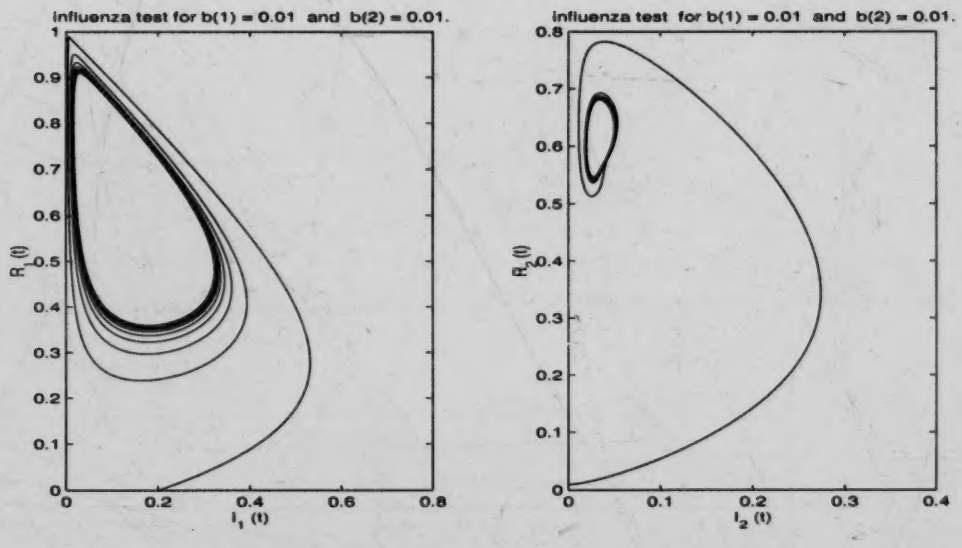


Figure 3.4: $i - r$ plane of two hosts cross infection with time delay term for $b_1 = 0.01$ and $b_2 = 0.01$.

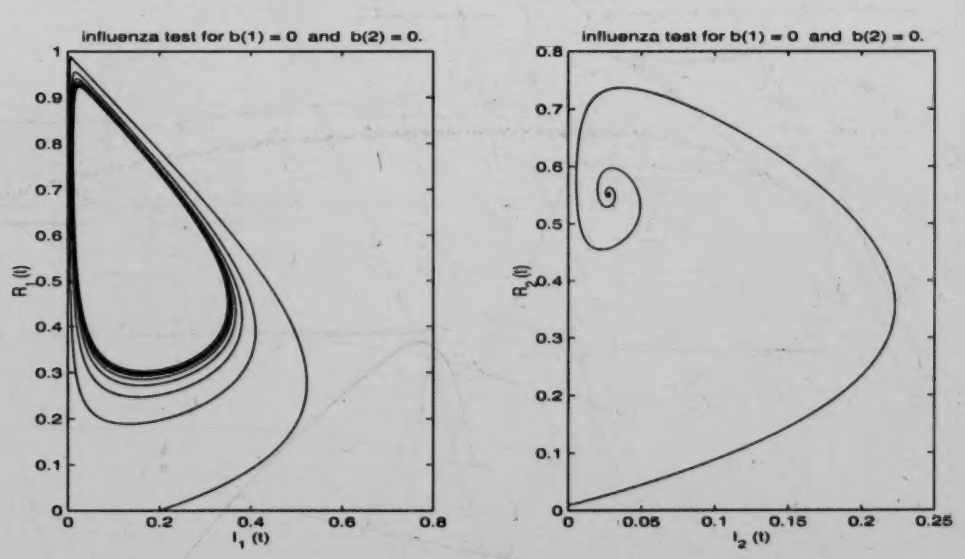


Figure 3.5: $i - r$ plane of two hosts cross infection with time delay term for $b_1 = 0.0$ and $b_2 = 0.0$

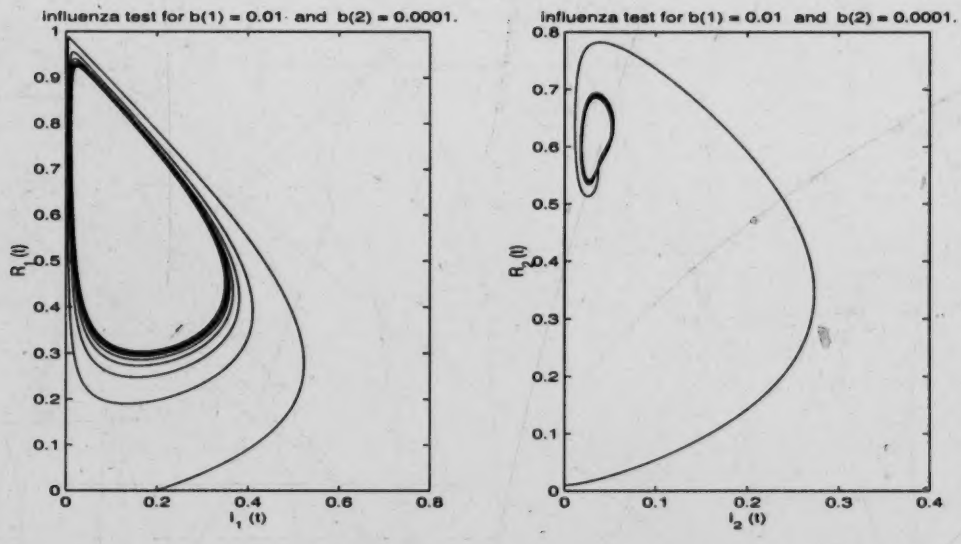


Figure 3.6: $i - r$ plane of two hosts cross infection with time delay term for $b_1 = 0.01$ and $b_2 = 0.0001$.

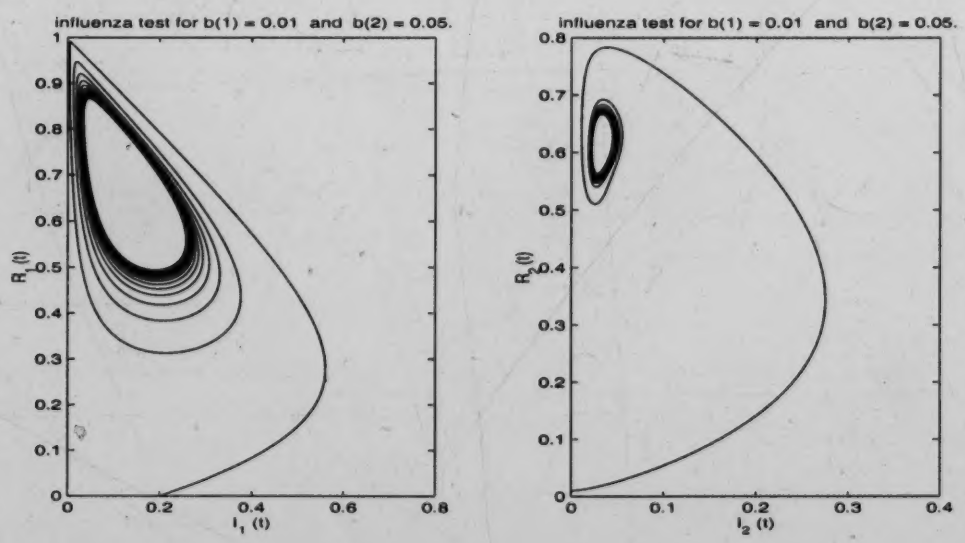


Figure 3.7: $i - r$ plane of two hosts cross infection with time delay term for $b_1 = 0.01$ and $b_2 = 0.05$.

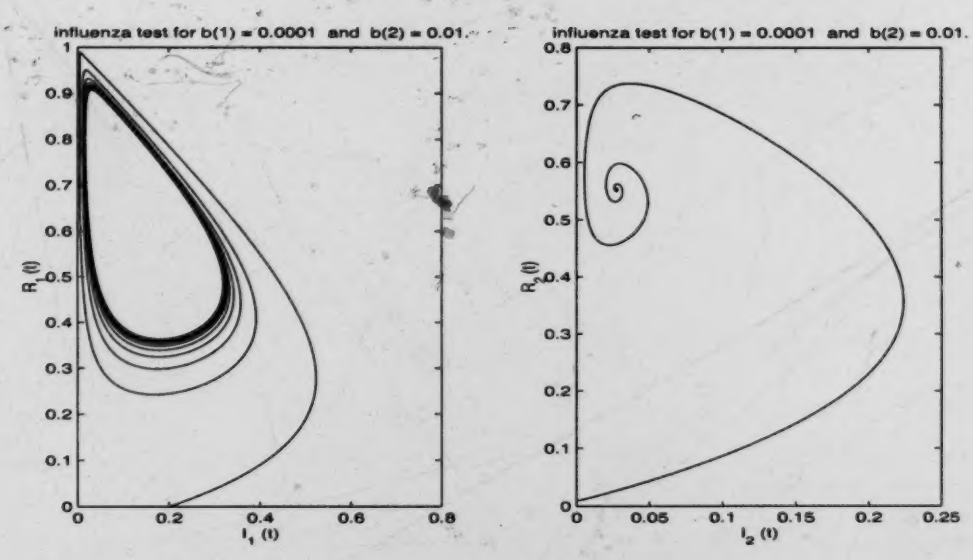


Figure 3.8: $i - r$ plane of two hosts cross infection with time delay term for $b_1 = 0.0001$ and $b_2 = 0.01$.

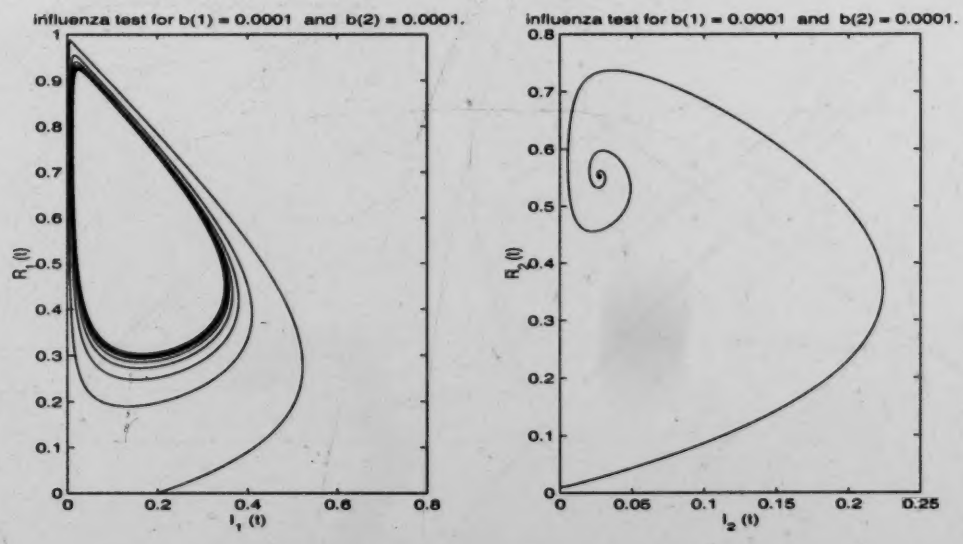


Figure 3.9: $i - r$ plane of two hosts cross infection with time delay term for $b_1 = 0.0001$ and $b_2 = 0.0001$.

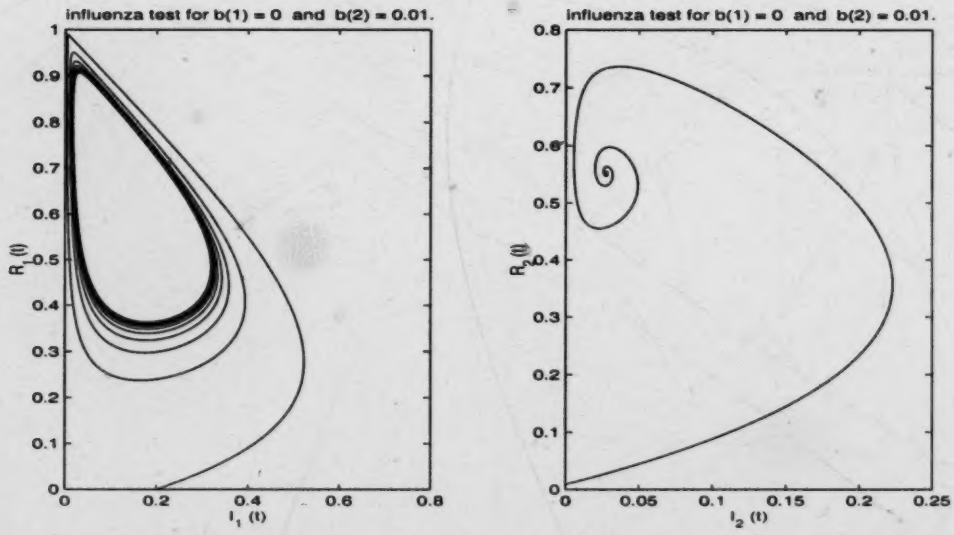


Figure 3.10: $i - r$ plane of two hosts cross infection with time delay term for $b_1 = 0.0$ and $b_2 = 0.01$.

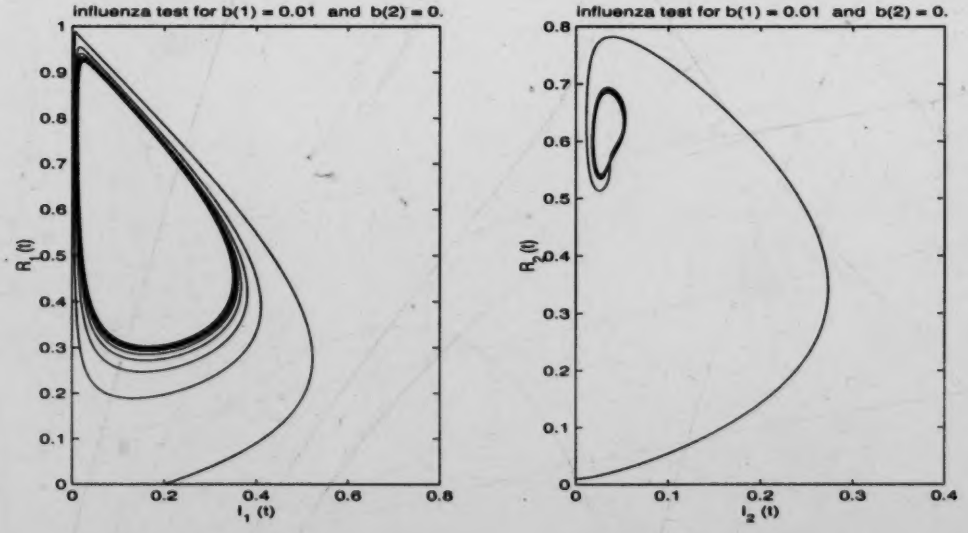


Figure 3.11: $i - r$ plane of two hosts cross infection with time delay term for $b_1 = 0.01$ and $b_2 = 0.0$.

Figure(3.12) to Figure(3.17) show i vs r graphs as μ_1 and μ_2 (see the diagram(1.1) change. There appears periodic solution. In those figures, one sees that there appears periodic solution in the second host as μ_1 and μ_2 change. For a fixed μ_1, as μ_2 increases, first the periodic solution in the second group appears but as μ_2 increases more, periodic solution becomes shrinking. As μ_1 increases, periodic solution in first group shrinks and disappears at last.

symbol	value	symbol	value
β_1	0.1	β_2	0.2
γ_1	0.02	γ_2	0.08
b_1	0.01	b_2	0.01
τ	300		

Table 3.2: Data of two SIRS system with varying μ_j for $j = 1, 2$.

3.3 Conclusion

In this Chapter, we show that single SIRS model with one delay term has periodic solutionfor some condition, which makes the other single SIRS model without delay term have periodic solution with cross infection. We use constant b_j here, but the model of coupled SIRS with one delay term has periodic solution numerically. From this result, we can see that There occurs oscillation of endemic in pig population with cross infection, which would not appear without cross infection. We conclude that cross infection sustains virus longer, which may explain why influenza virus appear without extinction. However, those model discussed in this thesis can be modified with considering cross infection between pig and avian species or including spatial ,seasonal and age effect.

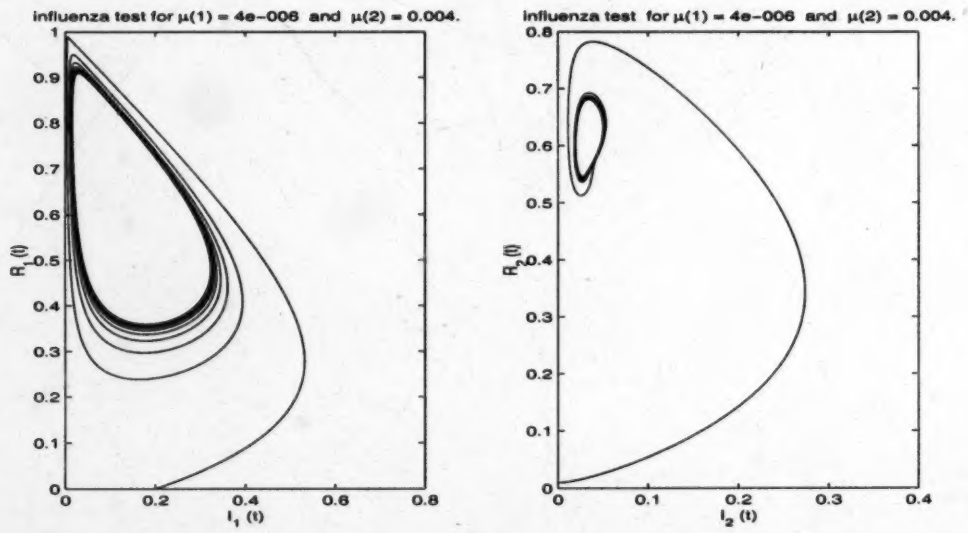


Figure 3.12: $i - r$ plane of two hosts cross infection with time delay term for $\mu_1 = 4 - 006$ and $\mu_2 = 0.004$.

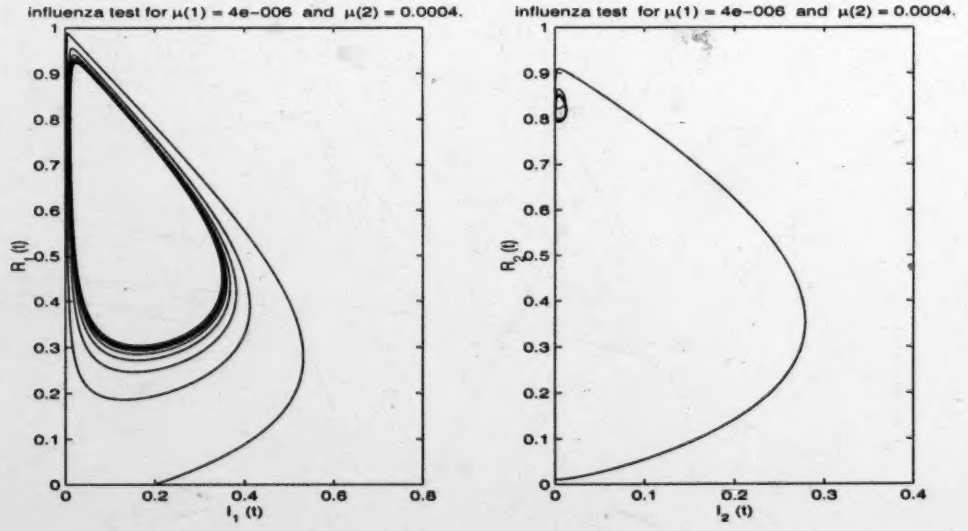


Figure 3.13: $i - r$ plane of two hosts cross infection with time delay term for $\mu_1 = 4 - 006$ and $\mu_2 = 0.0004$.

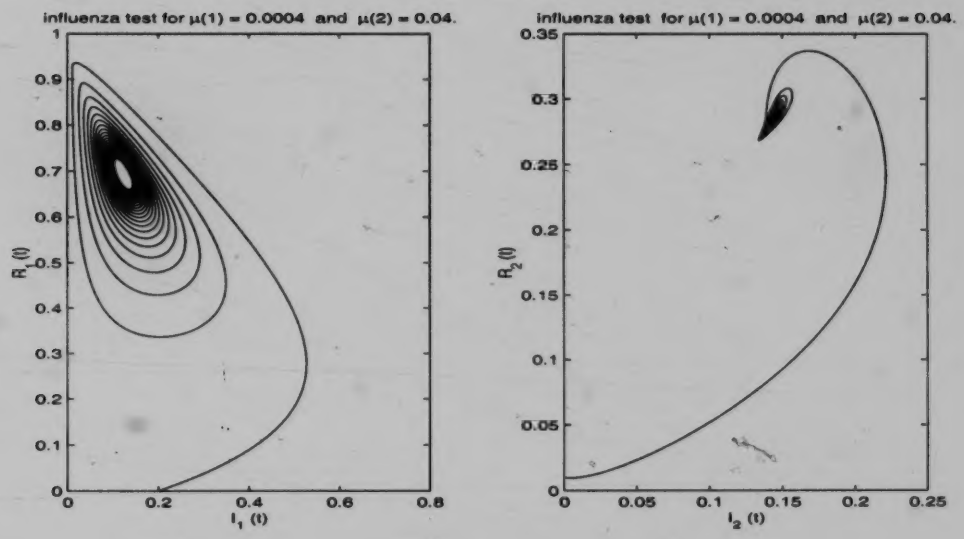


Figure 3.14: $i - r$ plane of two hosts cross infection with time delay term for $\mu_1 = 0.0004$ and $\mu_2 = 0.04$.

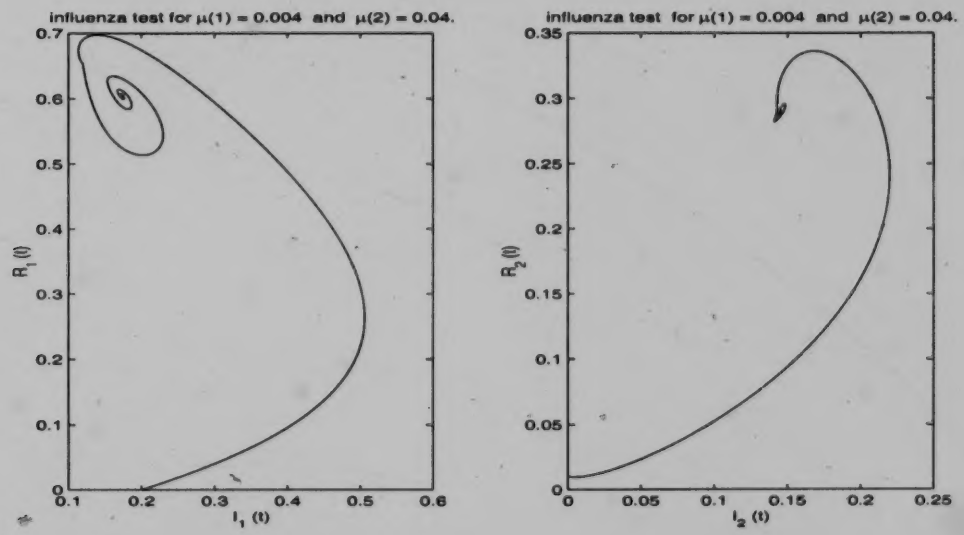


Figure 3.15: $i - r$ plane of two hosts cross infection with time delay term for $\mu_1 = 0.004$ and $\mu_2 = 0.04$.

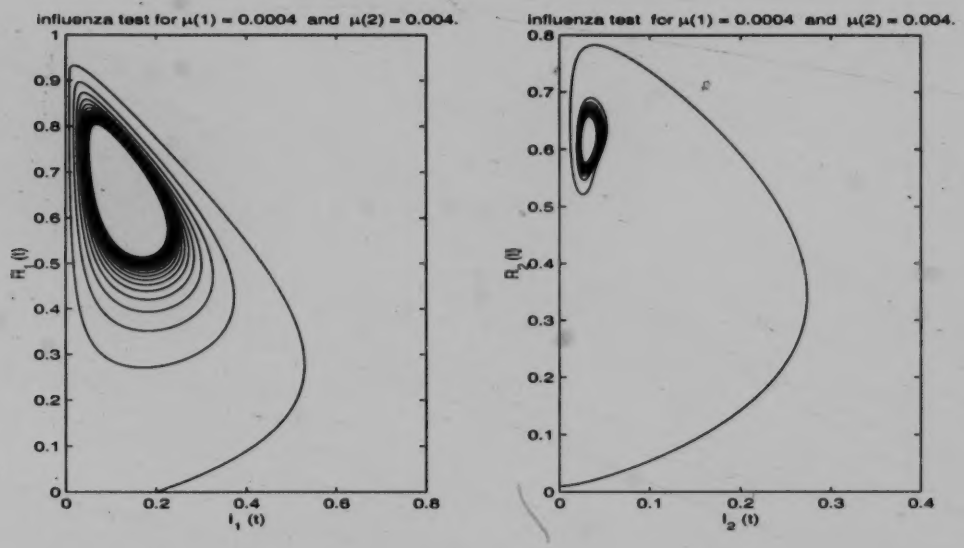


Figure 3.16: $i - r$ plane of two hosts cross infection with time delay term for $\mu_1 = 0.0004$ and $\mu_2 = 0.004$.

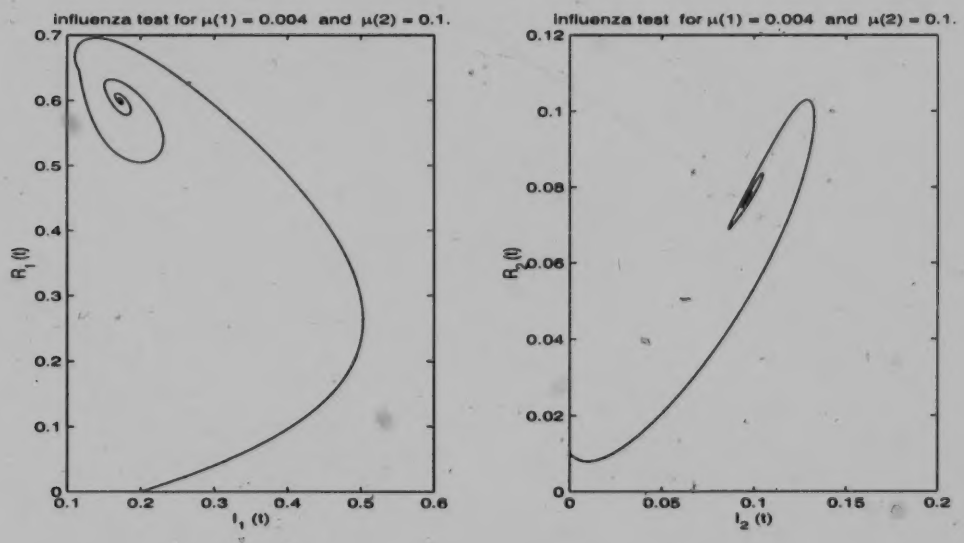


Figure 3.17: $i - r$ plane of two hosts cross infection with time delay term for $\mu_1 = 0.004$ and $\mu_2 = 0.1$.

Appendix A

Definitions and Theorems

Consider a system of autonoumous ordinary differential equations

$$x' = f(x), \tag{A.1}$$

where $f : D \to R^n$ is a C^1 map and $D \subset R^n$ is open.

Theorem. (Dulac's Criteria) [41, 49] Let $f \in C^1(E)$ where E is a simply connected region in R^2. If there exists a function $B \in C^1(E)$ such that $\nabla \cdot (Bf)$ is not identically zero and does not change sign in E, then (A.1) has no closed orbit lying entirely in E. If A is an annular region contained in E on which $\nabla \cdot (Bf)$ does not change sign, then there is at most one periodic orbit of (A.1) in A.

Theorem. (Poincaré–Bendixson Theorem) [41, 49]. Suppose that (A.1) is a relatively prime analytic system in an open set E of R^2 and that (A.1) has a trajectory Γ with Γ_+ contained in a compact subset F of E. Then it follows that $\omega(\Gamma)$ is either a critical point of (A.1), a periodic orbit of (A.1), or a graphic of (A.1).

Definition. [30, 41]. Let $\varphi(t, x_0)$ denote the flow of the differential equation (A.1) defined for all $t \in \mathbf{R}$ such that $\varphi(0, x_0) = x(0) = x_0$. An equilibrium point

$\overline{x} \in D$ of (A.1) is *stable* if for all $\varepsilon > 0$ there exists a $\delta > 0$ such that for all $x \in N_\delta(\overline{x})$ and $t \geq 0$ we have

$$\varphi(t, x) \in N_\varepsilon(\overline{x}). \tag{A.2}$$

The equilibrium point $\overline{x}$ is unstable if it is not stable. And $\overline{x}$ is *asymptotically stable* if it is stable and if there exists a $\delta > 0$ such that for all $x \in N_\delta(\overline{x})$ we have

$$\lim_{t \to \infty} \varphi(t, x) = \overline{x}. \tag{A.3}$$

$\overline{x}$ is *globally stable* on D if for all $x \in D$ of (A.1) we have

$$\lim_{t \to \infty} \varphi(t, x) = \overline{x}. \tag{A.4}$$

Theorem. (The Routh–Hurwitz) [8, 52] Either of the following conditions is necessary and sufficient for zero of the real polynomial

$$f(z) = a_0 z^n + a_1 z^{n-1} + \cdots + a_n \quad (a_0 > 0) \tag{A.5}$$

to have negative real part:

$$(i) a_n > 0,\ a_{n-2} > 0,\ a_{n-4} > 0, \cdots ; H_{n-1} > 0,\ H_{n-3} > 0, \cdots \tag{A.6}$$

$$(ii) a_n > 0,\ a_{n-1} > 0,\ a_{n-3} > 0, \cdots ; H_{n-1} > 0,\ H_{n-3} > 0, \cdots , \tag{A.7}$$

where H is the square matrix of the nth order:

$$\mathbf{H} = \begin{pmatrix} a_1 & a_3 & a_5 & \cdots & 0 \\ a_0 & a_2 & a_4 & \cdots & 0 \\ 0 & a_1 & a_3 & \cdots & 0 \\ 0 & a_0 & a_2 & \cdots & 0 \\ 0 & 0 & a_1 & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \cdots & a_n \end{pmatrix}. \tag{A.8}$$

The index of the coefficients decreases by one along a column, and increases by two along a row. The element h_{ij} is:

$$\begin{aligned} h_{ij} &= a_{2j-1} \text{ if } 0 \leq 2i - j < n, \\ &= 0 \qquad \text{if } 2i < j \text{ or } 2i - j > n. \end{aligned} \tag{A.9}$$

Definition. The kth order principal minors of an $n \times n$ matrix H are the determinants of the $k \times k$ matrices obtained by deleting $n - k$ rows and the corresponding $n - k$ columns of H (where $k = 1, \cdots, n$).

Definition. The kth order leading principal minor of the $n \times n$ matrix $H = (hij)$ is the determinant of the matrix obtained by deleting the last $n - k$ rows and columns of H (where $k = 1, \cdots, n$).

The leading principal minors $H_1, H_2, \cdots, H_n$ of H are the determinants:

$$\mathbf{H_k} = \begin{vmatrix} a_1 & a_3 & \cdots & \\ a_0 & a_2 & \cdots & \\ 0 & a_1 & \cdots & \\ \vdots & \vdots & & \\ 0 & 0 & \cdots & a_k \end{vmatrix}, k = 1, 2, \cdots, n. \tag{A.10}$$

(e.g. $n = 2, 3, 4$)

$n = 2$	$a_0 z^2 + a_1 z + a_2$	$a_2 > 0, a_1 > 0.$
$n = 3$	$a_0 z^3 + a_1 z^2 + a_2 z + a_3$	$a_3 > 0, a_2 > 0, a_1 a_2 > a_0 a_3$
$n = 4$	$a_0 z^4 + a_1 z^3 + a_2 z^2 + a_3 z + a_4$	$a_4 > 0, a_2 > 0, a_1 > 0, a_3(a_1 a_2 - a_0 a_3) > a_1^2 a_4$

Table A.1: Special cases of the Routh-Hurwitz theorem for $n = 2, 3, 4$.

Lemma. (Another criteria for the stability of matrices) [31, 29]. Let A be an $m \times m$ matrix with real entries. For A to be stable, it is necessary and

sufficient that

1. The second compound matrix $A^{[2]}$ is stable,

2. $(-1)^m det(A) > 0$.

Note that for the definition of the second compound matrix see the above reference.

For example, for $m = 4$, the second compound matrix $A^{[2]}$ of a 4×4 matrix $A = (a_{ij})$ is

$$\mathbf{A^{[2]}} = \begin{pmatrix} a_{11}+a_{22} & a_{23} & a_{24} & -a_{13} & -a_{14} & 0 \\ a_{32} & a_{11}+a_{33} & a_{34} & a_{12} & 0 & -a_{14} \\ a_{42} & a_{43} & a_{11}+a_{44} & 0 & a_{12} & a_{13} \\ -a_{31} & a_{21} & 0 & a_{22}+a_{33} & a_{34} & -a_{24} \\ -a_{41} & 0 & a_{21} & a_{43} & a_{22}+a_{44} & a_{23} \\ 0 & -a_{41} & a_{31} & -a_{42} & a_{32} & a_{33}+a_{44} \end{pmatrix}. \tag{A.11}$$

Definition. [17, 41, 49] A function $V : D \to \mathbf{R}$ satisfying the following properties is called a *Lyapunov function.*

Let $\overline{x}$ be a equilibrium of (A.1).

1. $V(x) > 0$ for all $x \in D \setminus \{\overline{x}\}$, and $V(\overline{x}) = 0$.

2. $V' < 0$ for all $x \in D \setminus \{\overline{x}\}$,

where

$$V'(x) = \frac{d}{dt} V(\varphi(t,x))|_{t=0} = \nabla V(x) f(x). \tag{A.12}$$

Theorem. (LaSalle's Invariance Principle) [38] Given (A.1), $V : D \to \mathbf{R}$, $V' \leq 0$ for $x \in D$. Let $S = \{x \in D : V'(x) = 0\}$. If the only complete trajectory which stays in S is $\overline{x}$, then (A.1) is *globally (asymptotically) stable* (i.e. all trajectories flow toward $\overline{x}$).

Theorem. (Global stability theorem) [30] Assume that

(H1) D is simply connected,

(H2) there is a compact absorbing set $K \subset D$,

(H3) x^* is the only equilibrium of (A.1) in D.

Under assumptions (H1), (H2), and (H3), x^* is a globally asymptotically stable in D if

$$\mu(A_f A^{-1} + A\frac{\partial f^{[2]}}{\partial x}A^{-1}) \leq -\delta < 0 \quad \text{on } K, \tag{A.13}$$

for some A, where A is a nonsingular $\binom{n}{2} \times \binom{n}{2}$ matrix–valued function $x \mapsto A(x)$ which is C^1 in D and a vector norm $|\cdot|$ on $\mathbf{R}^{\binom{n}{2}}$ and let μ be the Lozinskii measure with respect to $|\cdot|$. $\frac{\partial f^{[2]}}{\partial x}$ is the second compound matrix of $\frac{\partial f}{\partial x}$, and A_f is obtained by replacing each entry a_{ij} in A by its directional derivative in the direction of f (i.e. if $A_f = (\alpha_{ij})$, then $\alpha_{ij} := \frac{\partial a_{ij}}{\partial x} \cdot f$).

Appendix B

Codes of numerical simulations

Software used in this thesis

dde23 (L. Shampine and S. Thompson) simulates a large class of functional differential equations (Matlab base).

DDE-BIFTOOL (K. Engelborghs) allows computation and stability analysis of steady state solutions, their fold and Hopf bifurcations and periodic solutions of differential equations with several fixed discrete delays (Matlab base).

XPPAUT (G.B. Ermentrout) simulates differential equations with several fixed discrete delays and allows limited stability analysis of steady state solutions of differential equations with several fixed discrete delays.

(see http://www.cs.kuleuven.ac.be/ koen/delay/software.shtml)

Campbell Maple program.

cminputs - this contains the user inputs to the programs an example is included in the file

cm.gen - this file contains the program to calculate the centre manifold of a (system of) delay equation(s)

nf.gen - this file contains the program to calculate the normal form coefficients for a dynamical system with pure imaginary or zero eigenvalues

(see http://conley.math.ualberta.ca/joso/software/sueann/)
Maple (Waterloo Maple Inc.) is a general purpose computer algebra system, designed to solve mathematical problems and produce high-quality technical graphics and incorporates a high-level programming language.

Matlab (MathWorks, Inc.) handles numerical calculations and high-quality graphics, provides a convenient interface to built-in state-of-the-art subroutine libraries, and incorporates a high-level programming language.

XPP CODE

lee.ode

#eross-infection.

par $b_1 = 7.0$ $b_2 = 8.0$ $\gamma_1 = 33.333$ $\gamma_2 = 33.333$

par $\mu_1 = 0.004$ $\mu_2 = 0.028$ $\delta_1 = 0.01$ $\delta_2 = 0.00$

par $\beta_1 = 37.66$ $\beta_2 = 40.0$

par $c1 = 0.00008$ $c2 = 0.0002$ $d1 = 0.0001$ $d2 = 0.00022$

$i_1' = (\beta_1 * i_1 + e_2 * i_2) * (1 - i_1 - r_1) - (\mu_1 + \gamma_1) * i_1$

$r_1' = \gamma_1 * i_1 - (\mu_1 + \delta_1) * r_1$

$i_2' = (\beta_2 * i_2 + e_1 * y1) * (1 - i_2 - r_2) - (\mu_2 + \gamma_2) * i_2$

$r_2' = \gamma_2 * i_2 - (\mu_2 + \delta_2) * r_2$

$e_1 = b_1 * max(min(g1, 1), 0)$

$g1 = (y1 - c1)^3/(d1 - c1)^3$

$e_2 = b_2 * max(min(f2, 1), 0)$

$g2 = (y2 - c2)^3/(d2 - c2)^3$

init $i_1 = 0.000001$ $i_2 = 0.000002$ $r_1 = 0.02$ $r_2 = 0.04$

@ maxstor=1500000

@ total=800

done

CM.GEN CODE

cminputs

BEGINFILE cminputs

This file defines inputs for cm.gen

Equation – Simple flu model with Delayed term

$x1'(t) = aa * x1(t) * (1 - x1(t) - x2(t)) - (bb + cc) * x1(t)$

$x2'(t) = cc * x1(t) - bb * x2(t) - cc * exp(-bb * t1) * x1(t - t1)$

Linearised equation

$x1'(t) = (aa - bb - cc - 2 * aa * i^* - aa * r^*) * x1(t) - aa * i^* * x2(t)$

$x2'(t) = cc * x1(t) - bb * x2(t) - cc * exp(-bb * t1) * x1(t - t1)$

quadratiques : $-aa * (x1(t))^2 - aa * x1(t) * x2(t)$ in eqn 1

#

#

Part I : Define system

#

sysdim:=2; # number of equations/variables in system

numdel:=1; # number of delays (0,1,...)

zerdel:=1; # presence (1) or absence (0) of nondelayed terms in rhs of equations

#

Define coefficients

#

Define linear terms of rhs of equation, using $x1$, $x2$, $x3$,... as variables

```
#     t1, t2, t3,... as delays
#
lin :=array(1..sysdim);
aa  := 0.1;
bb  := 0.000004;
cc  := 0.02;
i*  := bb * (aa - (bb + cc))/(aa * (cc * (1 - exp(-bb * t1)) + bb));
r*  := 1 - (bb + cc)/aa - i*;
lin[1] := (aa - bb - cc - 2 * aa * i* - aa * r*) * x1(t) - aa * i* * x2(t);
lin[2] := cc * x1(t) - bb * x2(t) - cc * exp(-bb * t1) * x1(t - t1);
#
#     Define nonlinear terms of rhs of equation, using x1, x2, x3,... as variables
#     t1, t2, t3,... as delays
#
nonlin:=array(1..sysdim);
nonlin[1] := -aa * (x1(t))^2 - aa * x1(t) * x2(t);
nonlin[2] := 0;
#
#     Part II : Define numbers of eigenvalues and eigenvectors
#
numzer: = 0;      # number of zero e-values (0 or 1)
numimg: = 1;      # number of PAIRS of pure imaginary eigenvalues (0,1,..)
#
#     Define order of approximation
#
quadratic1 :=true;
cubic1 :=true;
```

```
quartic1 :=true;
quintic1 :=false;
#
#     Define simplifying equations at bifurcation point
#     This can significantly speed up computations
#
simpres := [cos(w1 * t1) = ((aa - bb - cc - 2 * aa * i* - aa * r*)
* (-bb) - (w1)^2 - (-aa * i*) * cc)/(aa * i* * cc * exp(-bb * t1)),
sin(w1*t1) = w1*((aa-bb-cc-2*aa*i*-aa*i*)-bb)/(aa*i**cc*exp(-bb*t1))];
#     cmdone determines whether coefficients of orginal dynamical system are
#     read in from the file coefs.gen or not
cmdone:=true;
#   ENDFILE cminputs
```

DDEBIF CODE

lee.m

```
clear;
% init system:
[name,n] = sys_init
% construct a first, approximate steady state point:
format long
stst.kind='stst';
stst.parameter=[10 0.004 2 3];
stst.x=[0.1148 0.6848]';
% get default method parameters for stst calculations:
method=df_mthod('stst')
```

```
method.stability.root_accuracy= 1.0000e-08
method.stability.minimal_time_step =0.001
method.stability.max_newton_iterations= 8
% correct the point:
[stst,success]=p_correc(stst,[],[],method.point)
stst.x
% compute its stability:
stst.stability=p_stabil(stst,method.stability);
% plot its stability:
figure(1); clf;
p_splot(stst);
% ask for roots with more negative real part:
method.stability.minimal_real_part=-0.5;
% recompute stability:
stst.stability=p_stabil(stst,method.stability);
% plot stability:
figure(2); clf;
p_splot(stst);
% get an empty branch with 1(β) as a free parameter:
branch1=df_brnch(1,'stst')
branch1.parameter
branch1.parameter.min_bound
branch1.parameter.min_bound(1,:)=[1 0];
branch1.parameter.max_bound(1,:)=[1 10];
branch1.parameter.max_step(1,:)=[1 0.2];
branch1.method.stability.minimal_time_step =0.001
branch1.method.stability.max_newton_iterations= 8
```

```
% use stst as a first branch point:
branch1.point(1)=stst;
% perturb and correct the point:
stst.parameter(1)=stst.parameter(1)-0.1;
[stst,success]=p_correc(stst,[],[],method.point);
% use as a second branch point:
branch1.point(2)=stst;
% set some continuation parameters:
branch1.method.continuation.plot=0;
% continue in one direction:
[branch1,s,f,r]=br_contn(branch1,100)
% turn the branch around:
branch1=br_rvers(branch1);
% continue in the other direction:
[branch1,s,f,r]=br_contn(branch1,100);
branch1.method.stability.minimal_real_part=-.5;
branch1=br_stabl(branch1,0,0);
% obtain suitable scalar measures to plot stability along branch:
[xm,ym]=df_measr(1,branch1);
% plot stability along branch:
figure(3); clf;
br_plot(branch1,xm,ym,'b');
ym
ym.subfield='l0';
br_plot(branch1,xm,ym,'c');
plot([0 10],[0 0],'-.');
plot( 2.068 , 0 ,'o');
```

plot(5.29 , 0 ,'o');
xlabel('β')
ylabel('R(λ)')
axis([0 10 -.05 0.05]);

sys_rhs.m

function f=sys_rhs(xx, par)

% xx : $x1$ $x2$
% par : β μ γ T
$f(1,1) = -((par(2)+par(3))*xx(1,1))+par(1)*xx(1,1)*(1-xx(1,1)-xx(2,1));$
$f(2,1) = par(3)*xx(1,1) - exp(-(par(2)*par(4)))*par(3)*xx(1,2) - par(2)*$
$xx(2,1);$
return;

DDE23 CODE

flu.m

$\beta(1) = 0.1;\ \beta(2) = 0.2;\ \mu(1) = 0.000004;\ \mu(2) = 0.004;\ \gamma(1) = 0.02;\ \gamma(2) = 0.08;$
$b(1) = 0.01;\ b(2) = 0.01;$ opts = ddeset('RelTol',$1e-8$,'AbsTol',$1e-8$); $\tau = 300$
sol = dde23('fluf',τ,'fluh',[0, 10000],opts,$\cdots$

$\beta, \mu, \gamma, b, \tau$); x = linspace(0, 10000, 400); figure subplot(2, 2, 1); plot(sol.y(1,:),sol.y(2,:))
title(['influenza test for $b(1)$ = ',num2str($b(1)$),' and $b(2)$ = ',num2str($b(2)$),'.'])
xlabel('I_1 (t)') ylabel('R_1 (t)') subplot(2, 2, 2); plot(sol.y(3,:),sol.y(4,:))
fluf.m

function $v = fluf(t, y, Z, \beta, \mu, \gamma, b, \tau)$

$ylag = Z(:, 1);$

$v = zeros(4, 1);$

$v(1) = (\beta(1) * y(1) + b(2) * y(3)) * (1.0 - y(1) - y(2)) - (\mu(1) + \gamma(1)) * y(1);$

if $t <= tau$

$v(2) = \gamma(1) * y(1) - \mu(1) * y(2);$

else $v(2) = \gamma(1) * y(1) - \mu(1) * y(2) - \gamma(1) * exp(-\mu(1) * \tau) * ylag(1);$

end

$v(3) = (\beta(2) * y(3) + b(1) * y(1)) * (1.0 - y(3) - y(4)) - (\mu(2) + \gamma(2)) * y(3);$

$v(4) = \gamma(2) * y(3) - \mu(2) * y(4);$

function $v = fluh(t, \beta, \mu, \gamma, b, \tau)$

$v = zeros(4, 1);$

$v(1) = 0.2;$

$v(2) = 0.0;$

$v(3) = 0.0001;$

$v(4) = 0.01;$

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